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ABSTRACT

In central serous chorioretinopathy (CSC), the macula is detached because of fluid leakage at the level of the retinal pigment epithelium. The fluid appears to originate from choroidal vascular hyperpermeability, but the etiology for the fluid is controversial. The choroidal vascular findings as elucidated by recent optical coherence tomography (OCT) and wide-field indocyanine green (ICG) angiographic evaluation show eyes with CSC have many of the same venous patterns that are found in eyes following occlusion of the vortex veins or carotid cavernous sinus fistulas (CCSF). The eyes show delayed choroidal filling, dilated veins, intervortex venous anastomoses, and choroidal vascular hyperpermeability. While patients with occlusion of the vortex veins or CCSF have extraocular abnormalities accounting for the venous outflow problems, eyes with CSC appear to have venous outflow abnormalities as an intrinsic phenomenon. Control of venous outflow from the eye involves a Starling resistor effect, which appears to be abnormal in CSC. Similar choroidal vascular abnormalities have been found in peripapillary pachychoroid syndrome. However, peripapillary pachychoroid syndrome has intervortex venous anastomoses located in the peripapillary region while in CSC these are seen to be located in the macular region. Spaceflight associated neuro-ocular syndrome appears to share many of the pathophysiologic problems of abnormal venous outflow from the choroid along with a host of associated abnormalities. These diseases vary according to their underlying etiologies but are linked by the venous decompensation in the choroid that leads to significant vision loss. Choroidal venous overload provides a unifying concept and theory for an improved understanding of the pathophysiology and classification of a group of diseases to a greater extent than previous proposals.

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1. Introduction

There are ocular diseases that appear to be related to venous outflow problems in the choroid (Spaide, 2020) Some of the pathophysiologic processes in these choroidal diseases appear to mirror those found in disease of other organ systems with chronic venous insufficiency (CVI). As such, the systemic examples of CVI may serve as an example for choroidal diseases, which include vortex vein occlusion, carotid cavernous sinus fistula (CCSF) and allied disorders, central serous chorioretinopathy (CSC), peripapillary pachychoroid syndrome, and spaceflight associated neuro-ocular syndrome (SANS). Each of these ocular diseases has somewhat different manifestations because of dissimilarities in underlying etiology, acuteness of onset, and amount of extraocular involvement, but appear to share venous overloading as a root cause. We present our unifying hypothesis of venous overload choroidopathy to describe several conditions in the eye and provide evidence from the literature in support of the hypothesis. We use examples of chronic venous insufficiency, common in other organs, as well as physical characteristics associated with flow in vessels to postulate the processes involved in the pathology of venous overload choroidopathy.

1.1. Chronic venous insufficiency and systemic disease

CVI is an extremely common malady in the body. The condition has several common pathophysiologic elements independent of the tissue or organ involved, whereas the final manifestations are organ-system specific. Although CVI may affect any organ system, one readily visible form involves the legs. Spider varicosities or telangiectasia (spider veins) represent dilated blood vessels visible through the skin and reticular varicosities affect smaller subcutaneous veins, particularly on the back of the leg. In the Edinburgh Vein Study, each of these was found in more than 80% of people in the age range of 18–64 years (Evans et al., 1999; Ruckley et al., 2008). Varicose veins were found in more than 30%. In the Vein Consult Program, an international prospective study of 91,545 people aged >18 years, some form of chronic venous disease in the legs was present in 84%. In addition to varicosities, venous insufficiency can cause hardening or thickening of the skin (lipodermatosclerosis) with alterations of pigmentation, ischaemia, and oedema. Advanced forms of CVI in the legs can lead to skin ulceration of the legs, with venous leg ulcers being the most common type of ulcer in the lower extremity (O'Donnell et al., 2014). The skin changes even can occur without varices being present. CVI may be either a primary condition or can occur secondary to other causes, such as following vein thrombosis, in a disease known as post-thrombotic syndrome. Examples of CVI affecting other parts of the body will be covered in Section 2.1.4.

1.1.1. Salient aspects of venous physiology

Postcapillary venules collect blood from capillaries; from the postcapillary venule, blood flows to increasingly larger venules and veins. At a minimum, the vein wall is comprised of endothelial cells and extracellular matrix. An increasing number of smooth muscle cells are found in bigger veins. Larger veins, including those in the face and orbits (J. Zhang and Stringer, 2010), may have bicuspid valves to prevent retrograde flow. Over a range, increasing pressure within the vein will cause a proportionate increase in the area of the lumen. In an erect human, the venous pressure in the head can be quite low, while the column of fluid pressure extends from the right atrium of the heart to the foot. The fluid pressure is calculated from the height of a fluid column, the density of blood, and the gravitational constant. With standing, the pressure in the veins of the foot can be 100 mm Hg. Along with the valves, muscle contractions, such as in the legs, help propel blood against gravity toward the heart, and when properly functioning, decrease venous pressure in the lower extremity. Vein wall composition varies according to body region and expected loading parameters, and involves variations in elastin, collagen, and muscle content and their architectural arrangement (Zócalo et al., 2013).

1.1.2. Pathophysiology of chronic venous insufficiency

A main feature central to the pathophysiology of CVI is increased venous pressure. This pressure increase may be the result of 1) increased amount of blood flowing through a vein, such as associated with an arteriovenous fistula, or because of 2) abnormalities in venous emptying, such as secondary to a venous thrombosis. Because CVI of the legs is so common, and the consequences of CVI potentially lead to surgery, pathologic specimens are readily available. In addition to macrovascular abnormalities, CVI is associated with a microangiopathy that worsens in proportion to the clinical severity of the CVI (Gschwandtner and Ehringer, 2001; Jünger et al., 2000). The skin shows decreased number of capillaries, which have a greater diameter. Because of the altered vascular architecture, CVI causes decreased transcutaneous partial pressure oxygen measurements, increased permeability of capillaries to low-molecular weight substances, tissue swelling, decreased vascular reserve (Saito et al., 2001), and low-grade inflammation (see Section 2.1.3).

1.1.3. Cellular and molecular factors in chronic venous insufficiency

In CVI, the vein wall is variably dilated and has reduced viscoelasticity. Increased hydrostatic pressure of an affected vein has been reported to lead to activation of integrins, induction of matrix metalloproteinases (MMPs) and increased MMP activity, particularly of MMPs 2 and 9 (Henke et al., 2007; Saito et al., 2001; Schwartz et al., 1999; Zamboni et al., 2005). This MMP activation enables breakdown of the extracellular matrix and increases the ratio of collagen type I to type III (Sansilvestri-Morel et al., 2003), potentially affecting tissue compliance. There may be an inflammatory cell infiltrate, which can result in the expression of a variety of cytokines and independently affect MMP expression (Grudzińska and Czuba, 2014; Nicolaides, 2005). In early stages of CVI, there are increased expression patterns of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 along with leukocytes that express lymphocyte function-associated antigen-1 and very late antigen-4. Expression of these markers persist through later stages of CVI, as determined by punch biopsies (Peschen et al., 1999). Mast cell involvement is common, particularly in cases of venous thrombosis (Budnik and Brill, 2018). In progressive stages of CVI, there are increased expression levels of platelet-derived growth factor receptor and vascular endothelial growth factor (Peschen et al., 1998). Moreover, there is overexpression of transforming growth factor beta, which is correlated with increased synthesis of nitric oxide synthase (Jacob et al., 2005; Kowalewski et al., 2010).

In the Starling principle of microvascular fluid exchange, hydrostatic pressure promotes fluid loss from the arterial end of the capillary, but fluid is resorbed by the venous end of the capillary and post-capillary venule because of decreased hydrostatic and increased osmotic pressure there. With excessive venous pressure, the hydrostatic pressure in the capillary is increased, leading to greater exudation from the vessels. In most tissues, interstitial fluid is returned by the lymphatic system within its functional capacity, but if overloaded, tissue swelling results. The lymphatic system is part of the circulatory and immune surveillance systems. Interstitial fluid is collected by a large network of lymph vessels that returns the excess interstitial fluid back to the heart, passing through lymph nodes that remove damaged cells and other debris. (George A.J.T., 2016) The lymphatic system is part of the circulatory and immune surveillance systems. Reappraisal of the Starling principle has led to the 'revised' Starling principle, which puts even more emphasis on the lymphatic return (Michel, 1997; Weinbaum, 1998). The effectiveness of venous return is compromised by venous insufficiency, which leads to pooling, inadequate function of any valves present, reflux in the flow through the vein or communicating channels, tissue swelling, and volume overload in the vascular systems being drained. The retention of blood in the venous system of an organ causes secondary changes in the vein that may be locally adaptive, but dysfunctional for

venous performance as a whole. Laplace's law for a cylinder, in this case a blood vessel, states the wall tension of the vessel is equal to the pressure across the vessel multiplied by the radius of the vessel (Westerhof N., Stergiopulos N., 2005). Venous dilation, even with the same internal pressure, leads to increased wall tension, which has the potential to set up self-reinforcing pathology.

1.1.4. Non-ocular systemic conditions related to chronic venous insufficiency

CVI is a disease process driven by venous hypertension resulting in venous dilation as a major component of the pathophysiology. Risk factors for CVI in the lower extremities include increased weight, height, positive family history, chronic standing, female sex, pregnancy, and a history of deep vein thrombosis (Fukaya et al., 2018). There is a very high proportion of bilateral concordance. The dilation and remodeling of the vein walls can be nonlinear and extreme, resulting in varicosities. Venous dilation and varicosity follow the same paradigm elsewhere in the body.

Pelvic congestion syndrome is associated with dilation and varicosities in the lower abdomen and pelvis. Analogous to CVI affecting the lower extremities, pelvic congestion syndrome results in venous pooling and increased venous backpressure for organs in the pelvis. The prevalence of pelvic congestion syndrome is estimated to be 15% in females aged 18–50 years (Brown et al., 2018). In men the syndrome is less commonly diagnosed but chiefly manifests by testicular varicocele, a common cause of male infertility (Alsaikhan et al., 2016). Advanced liver disease such as cirrhosis causes an increased gradient between the portal vein and the inferior vena cava. The normal difference can be up to 4 mm Hg, but with pressures in excess of 10 mm Hg, varices at various sites develop. The seemingly small pressure increase has the potential to divert flow through veins in the gastrointestinal tract and can lead to esophageal, gastric, duodenal, colonic, and rectal varices, among others (Sharma and Rameshbabu, 2012).

Arteriovenous fistulas divert arterial flow into veins, increasing the pressure and flow in the veins; splenic, mesenteric, and hepatic arteriovenous fistulae all are causes of esophageal varices (J. das Gupta et al., 2019; Harada et al., 1975; Law et al., 2012). Intracranial fistulas can lead to cerebral varices. Venous dilation, and occasionally varix formation, is a consequence that has been described in numerous organ systems, such as the brain, stomach, and pancreas (Chakraborty et al., 2010). Acquired pulmonary vein varices occur in the setting of pulmonary venous hypertension, mitral valve regurgitation, or end-stage liver disease and portal hypertension (AlNuaimi et al., 2018; Katoh et al., 1991; Palkar et al., 2015). Pressure overload from thrombosis also is a cause of venous dilation and varix formation in the lower extremities but is also found in the stomach after splenic vein thrombosis (Stone et al., 2014), portal hypertension and its associated varices following portal vein thrombosis, and small bowel varices secondary to chronic mesenteric vein thrombosis (Garcia et al., 2015).

1.2. Summary of the systemic manifestations of chronic venous insufficiency

Increased venous pressure, secondary to either increased flow or outflow obstruction, can lead to venous dilation and excessive fluid loading of veins and may induce a group of effects including expression of integrins, MMPs, and cytokines, that result in venous wall dilation, not just from fluid loading, but also from remodeling. The increased back pressure common to these conditions increases the hydrostatic pressure in the vessels being drained and also decreases the perfusion pressure. Pathologic changes in affected tissue include capillaries that have decreased number, but increased length and diameter. The increased magnitude and decreased gradient of intravascular pressure and the capillary anomalies lead to leakage, fluid imbalances, and oxygen delivery abnormalities to tissues (Thum et al., 1996). We will now discuss venous outflow from the choroid and how the anatomy of the choroid can influence the features that develop.

2. Venous outflow from the choroid

2.1. Salient vascular anatomy of the choroid

The choroid exhibits some differences from other vascular beds in the body. The arterial blood supply is delivered to the choriocapillaris by an efficient mechanism of the posterior ciliary artery branching into, usually, the medial and lateral posterior ciliary arteries (Spaide, 2020). Some people have three branches. The regions between adjacent branches can be seen as areas of delayed filling during fluorescein angiography and are referred to as physiologic watershed zones (Fig. 1). Variations in these watershed zones have been observed and are believed to result from variations in the vascular branching pattern and density, as influenced by the shape of the eye. These vascular branches form short posterior ciliary arteries, which perforate the sclera to feed the choroid at distributed sites. Branching within the choroid delivers blood to the choriocapillaris in a segmental fashion; there are very few anastomotic connections between the arterial branches. The choriocapillaris is a sheet of interconnected capillaries in which the flow is determined by the local pressure gradients established by feeding arterioles and draining venules. The blood is collected by venules, which feed into larger vessels. These larger vessels then continue directly to the ampulla of the vortex vein without further commingling with equal order veins. In particular, the larger veins do not combine to form large truncal veins within the choroid. The choroidal veins within an individual vortex system do not show the fractal branching structure found in other vessel systems, such as the retina. Instead, there are dozens of vessels that independently course toward the ampulla (Fig. 2).

2.1.1. Lack of lymphatic vessels in the choroid

Evaluation of the choroid with a battery of lymphatic markers has shown there is immunoreactivity for some of the markers by isolated, small cells (Schrödl et al., 2015). The cells were not connected in or to channels. Thus, there are no demonstrable lymphatic vessels in the choroid that have drainage connections to the lymphatic system. The lack of a lymphatic drainage system is thought to contribute to the immune privilege of the eye (Streilein, 2003).

A glymphatic system has been reported in the brain; this system is in neural tissue, modulated by glial cells expressing aquaporin 4, under control of the blood-brain barrier, and communicates with the cerebrospinal fluid (CSF) (Jessen et al., 2015; Rasmussen et al., 2018). The choroid does not have the same embryological precursors as the brain and does not have internal barrier functions to the diffusion of molecules. The choroid also lacks glial cells with aquaporin 4 expression surrounding vessels, and does not connect to a surrounding bath of fluid (Hamann et al., 1998; Nickla and Wallman, 2010). In the brain the glymphatic system helps remove molecules from the parenchymal tissue, but it does not manage excess fluid. Taken together these factors suggest the choroid is not likely to have a functional glymphatic system, and even if it were present in a rudimentary state, a choroidal glymphatic system would not remove excess fluid from the choroid.

2.1.2. Fluid movement from the subretinal space

The retinal pigment epithelium (RPE) and choroid are integral in maintaining the virtual subretinal space and to prevent separation of these two neuroectodermal layers, often called a 'retinal detachment'. The bare RPE is estimated to be able to remove 3.5 ml of fluid per day (Chihara & Nao-i, 1985). Subretinal blebs in experimental animal models are resorbed (Frambach and Marmor, 1982) more quickly if the RPE is damaged, and if the underlying RPE is damaged, the rate of resorption is faster (Negi & Marmor, 1983, 1984a, 1984b). This suggests the vector of fluid flow from the subretinal space to the choroid is not dependent on RPE pump function. Intravenous administration of hyperosmotic agents increases the speed of subretinal bleb resorption,

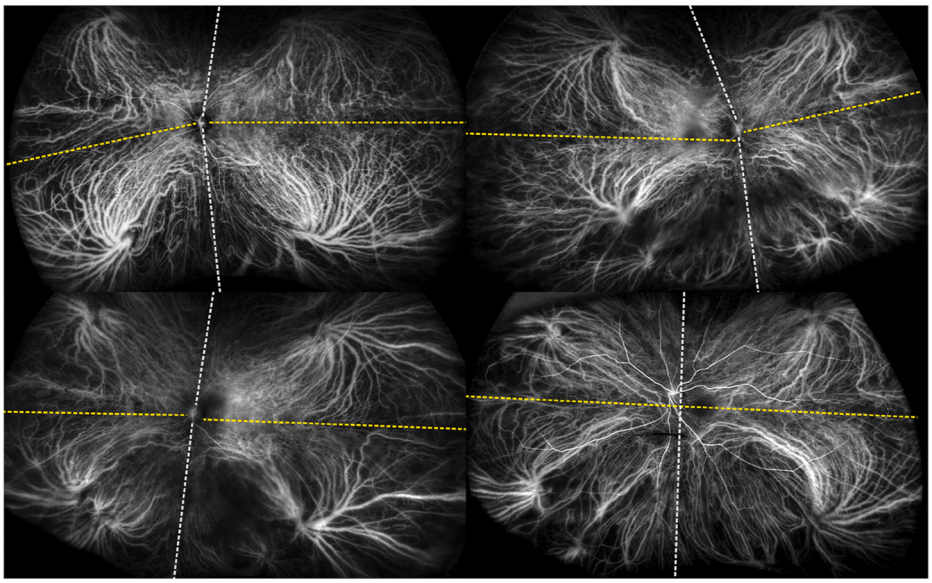

Fig. 1. These are 4 examples of normal patterns in wide-field indocyanine green ICG angiography of the choroid. The white lines delineate the watershed zones between the temporal and nasal aspects while the yellow line shows the watershed zone between the inferior and superior zones. These eyes appear fairly symmetrical quadrants even though there may be more than one vortex vein per quadrant. Some eyes have asymmetrical regions, but do not necessarily have disease.

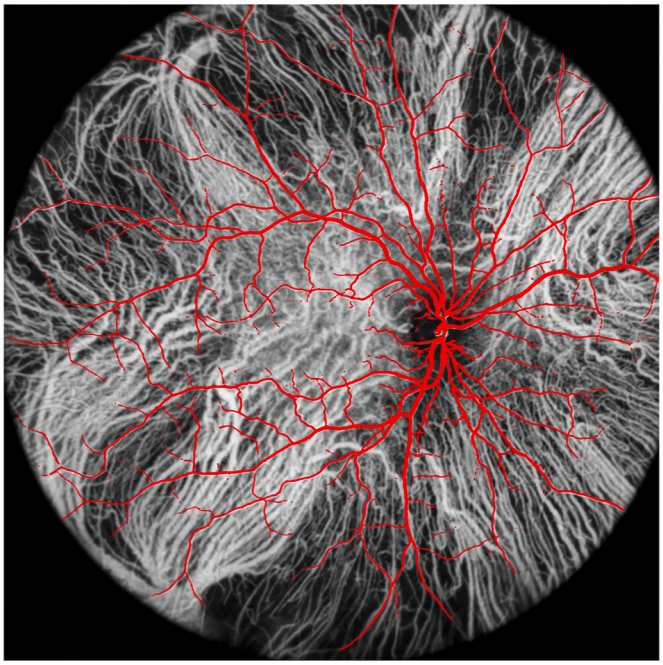

Fig. 2. Retinal and choroidal circulation in a normal subject. The image of the retinal vessels was obtained from a fluorescein angiogram. The image was binarized and overlaid in red on a registered image of the choroidal circulation obtained with indocyanine green (ICG) angiography. The retinal circulation follows a fractal pattern while the choroidal veins deviate from this strategy to form many parallel pipes.

suggesting the fluid is ultimately removed from the eye by vascular means, i.e. the choroid (Negi and Marmor, 1983). These findings are consistent with the choriocapillaris abiding by the original Starling hypothesis. This strategy is efficient, as the need for any lymphatic drainage would be decreased.

2.2. Control of venous outflow

The fractal-based branching of vessels, as defined by Murray's law (Murray, 1926a, 1926b), has been shown to be the most efficient mode for blood distribution. The choroidal venous system deviates from what ostensibly is the "most efficient" as it shows a parallel pipe arrangement. When these deviations occur in nature, it is generally because there are other variables that are also being optimised (Spaide, 2020). Suggested reasons for the retention of many parallel pipes instead of an increasing large pipe generated by merging of veins include: to improve the heat sink capability of the choroid; to help maintain independence of groups of choriocapillaris lobules; to retain a store of oxygen in the choroid; and to help modulate intraocular pressure (IOP) in the eye during pulsatile inflows of arterial blood (Spaide, 2020). The eye has a very high blood flow rate, much like the brain. Both the intraocular contents and the brain have tough outer shells, the sclera and skull respectively, and these shells have limited distensibility.

2.2.1. Starling resistor in the brain

In the brain, the potential pressure rise is mediated by movement of the CSF and by controlling the release of stored blood in the venous system. The bridging cerebral veins that enter the superior sagittal sinus have their flow controlled in part by the pressure of the CSF, through which they course. If the CSF pressure is higher than the venous pressure, the veins collapse and do not allow outflow from the brain. During the complex movement of fluid in the skull and spinal cord during systole, the increasing pressure in the veins exceeds the pressure in the CSF and bridging vessels open and allow flow into the superior sagittal sinus. The control of flow in a tube by external forces creates what is known as a Starling resistor (Bertram, 1995; Knowlton and Starling, 1912; Spaide, 2020). The CSF pressure can be below the physiologic range, such as when a ventriculoperitoneal shunt has a pressure set point that is too low. In this situation, there is excessive venous drainage from the brain because there is inadequate control of venous outflow through the Starling resistor mechanism of the cerebral veins. Affected patients develop postural headaches, cognitive difficulty, and a host of other neurologic symptoms, and these are relieved by increasing the CSF pressure (Barami, 2016; Barami and Sood, 2016).

2.2.2. Starling resistor in the choroid

The venous pressure in the eye is slightly below that in the choriocapillaris. Both are slightly greater than the IOP. The pressure in the vortex vein outside of the eye is approximately 3–4 mm Hg (Bill, 1962, 1985). Intuitively, that would imply increasing the IOP by a small amount could cause the choriocapillaris and then the larger choroidal veins to collapse, subsequently stopping flow in the vortex vein outside the eye. However, that does not happen (Mäepea, 1992) (Fig. 3). If the IOP is increased, the choriocapillaris pressure increases, as does the pressure in the larger veins, the outflow through the vortex vein outside of the eye continues to be 3–4 mm Hg. The pressure in the choroidal veins shows an extraordinary linear relationship with the IOP, always being slightly higher than the IOP. Within this pressure range, outflow is maintained in the vortex vein. That is, until the IOP equals the systolic pressure, at which point the flow in the vortex vein outside of the eye stops (Mäepea, 1992). This process appears to be entirely passive, and thus is likely to be controlled by a Starling resistor mechanism. The IOP can exceed 200 mm Hg during scleral buckling surgery (Gardner et al., 1993), but it is uncommon to see the vortex veins blanch. The implication is that there appears to be a control of the outflow of blood from the choroid, even if the IOP is well above the physiologic range. This control must occur between the choroidal veins and the vortex veins outside of the eye, since the pressure in the vortex vein remains at a relatively low and constant level. Analysis of pressure measurements by Bill in rabbit eyes showed that the pressure in the vortex vein was low when measured at the scleral border as the vortex vein left the eye (Bill, 1962). This implies the control region of the Starling resistor must be at either the ampulla or outflow through the sclera.

A varix of a vortex vein is an extreme enlargement of the ampulla. By increasing the IOP with scleral depression, for example, the varix will collapse over a period of 20–30 s. The vortex veins do not collapse. With release of the pressure from the scleral depression the varix will reinflate over a period of 20–30 s (Gündüz et al., 1998). This suggest, at least for these eyes, there may be two separate points of control of the Starling resistor, one at the outflow of the varix, but also another one at where the vortex veins lead into the varix.

The control of venous outflow may be related to architectural arrangement of the initiation of the vortex vein. The vessel courses through the sclera at an angle similar to that used to make self-sealing incisions in vitrectomy surgery (Fig. 4). With self-sealing incisions, the tunnel of the opening is sealed by a valve-like closure of the inner leaf against the outer wall of the eye. An analogous situation may occur with the exit of the vortex vein. Increased IOP would put a correspondingly larger pressure on the inner side of the tunnel, squeezing the exiting vein. This passive mechanism may help modulate the outflow resistance for venous flow.

3. Venous overload of the choroid and its consequences

3.1. Choroidal venous overload from systemic venous problems

Elevated venous pressure can occur in the superior vena cava as the result of right heart failure, pulmonary hypertension, malignant tumors in the mediastinum, and dilated cardiomyopathies (Elzanaty et al., 2020; Talapatra et al., 2016; Zimmerman and Davis, 2018). The ocular manifestations are complex as the increased venous back pressure affects the retina and choroid. The effects on the retinal circulation include venous dilation, vascular tortuosity, macular oedema, and central retinal vein occlusion (Lewczuk et al., 2019). The effects on the choroidal circulation include serous detachment of the retina, choroidal and ciliary body detachment, angle closure glaucoma and transient myopia (Fujitani and Hayasaka, 1995; I. Gupta et al., 2020; Krohn & Bjune, 2003; Lewczuk et al., 2019; Senthil et al., 2009). Li and coworkers reported a case of multifocal CSC in a patient with untreated inherited pulmonary arterial hypertension and right heart failure. The patient had marked choroidal thickening as imaged by enhanced depth imaging (EDI) optical coherence tomography (OCT) that improved with treatment of the medical issues. Of interest is the indocyanine green (ICG) angiogram that showed what appeared to be intervortex venous anastomosis (in their Fig. 3) (X. Q. Li et al., 2015). The authors proposed the choroidal venous stasis and diffuse choroidal thickening were caused

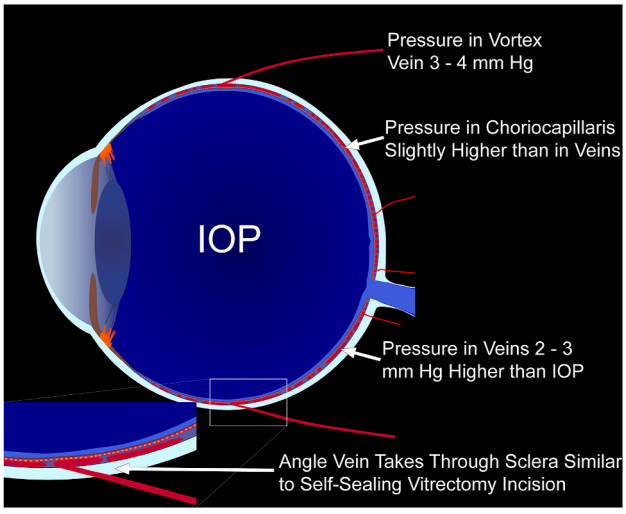

Fig. 3. Intriguing aspects of venous drainage of the choroid. The pressure in the choriocapillaris is slightly higher than the intraocular pressure (IOP) and the pressure in the larger choroidal vessels. This would imply an increase in IOP could easily interrupt flow in the choriocapillaris and the choroidal veins. However, increasing IOP is met with proportionate increases in the choriocapillaris and venous pressure. This appears to be a passive process and responsive over a large range of pressures. Of interest is the pathway of the vortex veins as they leave the eye. They follow the same trajectory as those used for self-sealing vitrectomy wounds. In those incisions the IOP is thought to cause the tunnel to close. This same mechanism may be at work in maintaining the venous outflow pressure from the choroid.

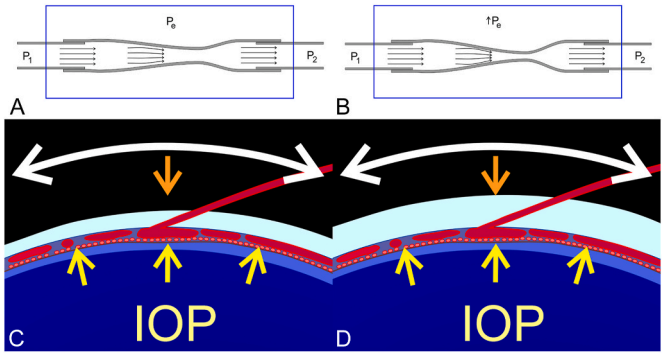

Fig. 4. Starling resistor. A. The amount of flow in a tube is a function of the pressure differential (P_1–P_2) and the resistance of the tube. In a Starling resistor the tube is flexible and exposed to a modulating force external to the tube P_e. Increasing P_e can cause constriction of the flexible tube (B). The ability to control flow in a tube by external application of pressure lies at the heart of a Starling resistor. C. The exist of a vortex vein from the eye follows an angled path. IOP can compress the inner aspect of the tunnel through which the vein passes. Increasing the IOP (yellow arrows) acts to push against the wall of the eye. Expansion of the sclera increases the circumferential stress (also known as hoop stress) in the lamellae of sclera (white double arrow). The resistance to expansion creates a vector (orange arrow), which affects the outer portion of the passageway for the vein. D. In nanophthalmic eyes, the scleral passageway is lengthened in proportion with the scleral thickness. Although not shown, myopic eyes have a thinner sclera (Pekel et al., 2015) and the pathway would be shorter. Of interest is the scleral thickness in men is greater than in females (Buckhurst et al., 2015; Read et al., 2016; Schlatter et al., 2015).

by elevated venous pressure.

3.2. Choroidal venous overload from regional problems

3.2.1. Carotid cavernous sinus fistula and allied disorders

A CCSF diverts blood flow from the carotid or one of its dural branches to the cavernous sinus, a honeycomb-like space on each side of the body of the sphenoid bone (Moini and Piran, 2020). There is a high flow when it comes directly from the internal carotid, also called a direct CCSF, and lower flow if the communication occurs through a dural branch, that is, an indirect CCSF. A direct CCSF generally develops from a traumatic tear in the internal carotid artery while an indirect CCSF is usually idiopathic. The signs and symptoms of indirect CCSF are similar to, but less severe than, those associated with direct CCSFs. An arteriovenous malformation (AVM) is a tangle of vessels in which there is a communication between the arteries and veins without intervening capillaries. AVMs may occur in the cavernous sinus or within the brain that drain into the cavernous sinus and cause cavernous sinus disease because their high flow output increases pressure within the cavernous sinus. Patients with a CCSF have pulsatile exophthalmos, chemosis with enlarged conjunctival and episcleral vessels, pain, decreased vision, palsies affecting the oculomotor or abducens nerves or both, and an ocular bruit. Orbital congestion with venous dilation occasionally leads to the development of superior ophthalmic vein varices, which may harbour a thrombosis (Bullock et al., 1990; Iseki et al., 2010). Vision loss is common in CCSF and may be related to decreased ocular perfusion because of alterations in the pressure gradient or to increases in the absolute pressure (Alam et al., 2019). The increased fluid pressure loading, and possible ischaemia may contribute to pre- and intra-retinal haemorrhages, macular oedema, optic disc hyperemia, vein engorgement and potentially central retinal vein occlusion.

Choroidal changes from CCSF, AVMs affecting blood flow in the cavernous sinus, and superior ophthalmic veins are related to the increased pressure and abnormalities in perfusion pressure. More modest changes include choroidal thickening and dilation of the choroidal veins and choroidal folds (González Martín-Moro et al., 2018; Inam et al., 2019; Rey et al., 2016; Shinohara et al., 2013). More advanced changes include serous retinal and retinal pigment epithelial detachments (Fuzzard et al., 2020), with leaks seen in fluorescein angiography that can resemble those seen in CSC. Severe cases can have serous detachment of the choroid. EDI-OCT has shown the choroid generally is thickened in patients with CCSFs. Dye-based angiography shows delayed filling of the choroid together with dilated choroidal veins. Remarkably, with surgical repair or spontaneous thrombosis of the fistula, the ocular abnormalities abate. The choroid becomes thinner and serous retinal detachments resolve (González Martín-Moro et al., 2018; Rey et al., 2016; Shinohara et al., 2013).

Sutoh and colleagues documented the marked changes of the choroidal circulation among patients with CCSF (Sutoh et al., 1996) (Fig. 5). After CCSF development, the choroidal veins showed variable dilation and pulsatile filling that was not synchronous over the expanse of the choroid. During follow-up, loss of some of the larger choroidal vessels occurred with an increase in the tortuosity of those remaining. There was a diminution in the size of the ampullas of the vortex veins and posterior drainage that was evidenced by larger choroidal veins which seemed to terminate near the disc. The eyes developed large intervortex venous anastomoses. Following the formation of the intervortex venous anastomoses, there was patchy filling defects in the choriocapillaris in the periphery.

Thrombosis in the cavernous sinus or superior ophthalmic vein may compound problems associated with CCSF by the decreased perfusion from the cessation of venous outflow (Carrim et al., 2007). The induced choroidal changes may be similar to those seen with a CCSF and can be associated with more pronounced vision loss (Kupersmith MJ et al., 1996).

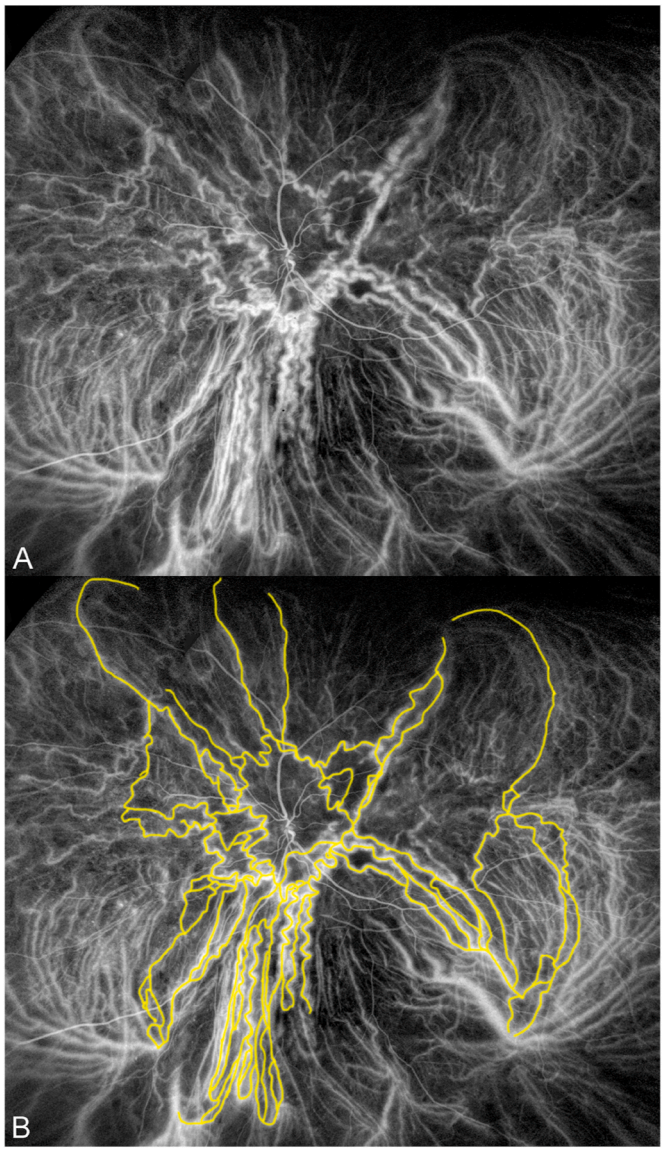

Fig. 5. Choroidal changes associated with carotid cavernous sinus fistula. A. There are prominent choroidal vessels that are intervortex venous anastomoses. These are highlighted in (B) in yellow. Image courtesy of Gerardo Ledesma-Gil.

3.2.2. Vortex vein occlusion

Mantel and coworkers reported 3 cases of choroidal changes from spontaneous vortex vein occlusion (Mantel et al., 2014). These patients had acute ocular pain associated with a transient localised haemorrhagic thickening of the choroid within the distribution of a vortex vein, as imaged by wide-field ICG angiography. In the subacute phase, the patients showed delayed arterial-venous filling. The findings resolved in 8–12 weeks.

Experimental occlusion of the vortex vein has been studied in animals for over 150 years with many of the earliest studies related to glaucoma and later studies examining the effects on the retina, RPE, and choroid (Sohan Singh Hayreh, 2015). The experimental occlusions were performed in otherwise young, healthy animals. Sachsenweger and Lukoff occluded the vortex veins in dogs. Rapid closure of one or two vortex veins resulted in dilated choroidal vessels in the regional distribution of their drainage. Closure of three or more caused a detachment of the retina (Sachsenweger and Lukoff, 1959). Kita et al. created small retinal detachments in rabbit eyes in which two vortex veins were ligated, and the fluid absorption time was prolonged to 138% of that in control eyes. By doing a concurrent partial thickness scleral resection,

the resorption time was reduced to 115% of the control eyes (Kita et al., 1990). The authors postulated that vortex vein occlusion increased choroidal tissue pressure, which inhibited resorption of the detachments. Scleral resection helped reduce the tissue pressure by allowing fluid to escape posteriorly and helped speed resolution of the retinal detachments.

Hayreh and Baine reported the findings induced in monkeys when one or more vortex veins were occluded (S.S. Hayreh and Baine, 1973). They found that the induced changes were proportional in extent and severity to the number of vortex veins occluded. Fluorescein angiography showed delayed choroidal filling in the sectors involved by occlusion. The watershed zones between the vortex vein systems were well defined and the last to fill with dye. To Hayreh (Sohan Singh Hayreh, 2015), this suggested a segmental nature of venous drainage of the choroid with there being very little communication between adjacent systems. After occlusion, swelling occurred in the affected area, and this resolved in 1–2 weeks. The exception, of sorts, may have been when all of the vortex veins were occluded, in which case the eye often had hyphema, narrowing of the angle and increased IOP, making these eyes difficult to evaluate and early evaluation in most animals, but later findings included thinning and chorioretinal atrophy near the equator (S.S. Hayreh and Baine, 1973).

Kadomoto ligated three vortex veins of the left eye and two in the right of rabbits. In these eyes, the RPE showed degenerative changes at 1 week that became more prominent at two weeks. The outer segments of the photoreceptors showed no ultrastructural changes if two vortex veins were ligated, but if three veins were occluded maximal changes were seen at three weeks. By 4 weeks, the changes reverted to normal (Kadomoto, 1989). Nishikawa and coworkers sutured and cauterized two vortex veins of each eye of 5 macaque monkeys. ICG angiography showed delayed filling along with slowed clearance of dye. The choroidal veins showed retrograde filling that was pulsatile (Nishikawa et al., 2008) in the area of the occluded vortex veins. Matsumoto and coworkers occluded all vortex veins of mice, and found that the choroid became thicker, the RPE showed focal degeneration, inflammatory response genes were upregulated, and macrophages were found in the choroid (Matsumoto et al., 2021).

Takahashi and Kishi evaluated patients with rhegmatogenous retinal detachment treated with scleral buckling; in 7 eyes, one vortex vein was occluded and in 5 eyes, two were occluded (Takahashi and Kishi, 2000). In 10 of the 12 eyes that had ICG angiography at 3 months to more than 1 year after retinal reattachment surgery, anastomotic connections between vortex vein systems were seen with connections between superior and inferior systems being the most common. These anastomotic connections were dilated connecting channels that violated the watershed zones between the vortex vein systems. The authors did not mention if PEDs were present.

Chen and colleagues occluded the vortex veins in 8 cynomolgus monkeys and followed the EDI-OCT findings over ensuing weeks (Chen et al., 2018). In Group A, both the superotemporal and inferotemporal vortex veins were occluded and in Group B only the inferotemporal vein was occluded. They found a regional fluorescein hyperfluorescence in the affected segments one day after occlusion, but these disappeared after one week. ICG angiography showed filling delays in the occluded quadrants in the first week, with hypofluorescence occurring in the late phase. The reported choroidal thickness changes seem to indicate thickening in the distribution of the occluded veins early, but by 12 weeks, the regions supplied by vortex veins that were not occluded also showed choroidal thickening. No mention was made of collaterals.

How well a model emulates a chronic disease depends on many factors. Changes in chronic diseases build slowly and may eventually reach a crescendo, typically in older individuals. (In addition, chronic diseases may not share all the features of an acute disease because homeostatic mechanisms have time to offset them.) CCSF and vortex vein occlusions differ from other conditions in this grouping because of the severity and acuteness of onset of vascular abnormalities. These changes induce choroidal venous dilation, intervortex venous anastomoses, engorgement of the choroid, and serous retinal detachment, but in the acute phases these conditions may also be associated with hemorrhages in the choroid, something that does not occur in CSC, for instance. Animal models of the same are performed in healthy animals, which may not experience the same findings of older humans who may have interactions with other pathologies associated with aging and develop disease manifestations over time.

3.2.3. *Uveal effusion syndrome*

In uveal effusion syndrome, originally described by Schepens and Brockhurst in 1963 (Schepens and Brockhurst, 1963), the eyes were found to have a retinal detachment without any breaks. No mention of refractive error or axial length was made in that article. Later Brockhurst described a new clinical entity, nanophthalmos with uveal effusion (Brockhurst, 1975), and in 1980 a new operation to treat the disorder (Brockhurst, 1980). Following a hypothesis by Shaffer, (Calhoun, 1975) who thought the detachments were due to “choroidal congestion due to impairment of venous drainage through extremely thick sclera”, Brockhurst decompressed the vortex veins. In his procedure, flaps of sclera overlying the vortex vein were removed. The sclera was noted to be more than 2 mm thick. In the original series of 10 eyes, the retina was reattached in 8 (Brockhurst, 1980). In a later publication by Trelstad, with Brockhurst as a co-author (Trelstad et al., 1982), the sclerae of eyes with nanophthalmos were found to be excessively thick, have perifibrillar aggregates of what appeared to be proteoglycans, and collagen fibers that were more disordered than that found in normal eyes.

Gass reported the outcome of two cases who were treated using a different technique (J. Donald M. Gass, 1983). Gass reasoned that the sclera was abnormally thick in uveal effusion and there was an impediment to the transport of protein and fluid across the abnormal sclera. His operation involved making sclera windows, which looked somewhat similar to those proposed by Brockhurst, but the flaps were in between the vortex veins. This procedure caused retinal reattachment in the two treated patients (J. Donald M. Gass, 1983). Although the stated intent of the operations was different, both involved resecting a significant thickness of the sclera, either located over the vortex veins or between them.

Uyama and colleagues summarised the possible pathophysiology of serous detachment in uveal effusion in a 2000 paper in which the excessive scleral thickness reduced the permeability of transscleral outflow and impeded vortex vein flow and caused congestion. The fluid accumulation in the choroid was proposed to cause a dysfunction in the pump mechanism of the RPE, which could lead to subretinal fluid accumulation (Uyama et al., 2000). Thus, some forms of uveal effusion syndrome may overlap with CSC, as will be presented in the next section.

In addition to affecting scleral outflow, the wall characteristics may influence vascular hemodynamics. The wall thickness and rigidity can be expected to alter the forces on vessels during the pulse cycle.

3.2.4. *Central serous chorioretinopathy*

CSC is a common disease world-wide (Kitzmann et al., 2008; Y. Li et al., 2016; Sahoo et al., 2019). and has fascinated ophthalmologists for decades. Over that time many different treatments have been proposed, while only few have been shown to work. CSC is a human disease with no animal analog, which prevented understanding of even basic features of the disease until more advanced imaging was developed. Each form of imaging provided new clues to the pathogenesis of CSC and related disorders. CSC causes circumscribed serous detachment of the retina secondary to leaks from the level of the RPE as seen with fluorescein angiography. Eyes with CSC may also have choroidal folds, PEDs, and granular changes in the pigmentation of the RPE, atrophy of the RPE and secondary neovascular complications. It is most commonly found in middle aged men with a male to female ratio of approximately 3:1 (Tittl et al., 1999). Typical presenting complaints are decreased vision, distortion, and persistent afterimages. Eyes with CSC do not have signs

of intraocular inflammation, accelerated hypertension, infiltration, or infarction, which are potential causes of exudative retinal detachment. The visual acuity can be improved with a low plus addition to account for the retinal elevation by the serous fluid.

The detachment of the retina usually involves the macula and appears as a smooth serous elevation with OCT imaging. If the detachment has been present for a month or longer there can be accumulation of what appears to be shed outer segments of the photoreceptors along the back surface of the detached retina (Spaide, 2007; R.F. Spaide and Klancnik Jr., 2005). Fluorescein angiography reveals one or more focal leaks from the level of the RPE and there may be detachments of the RPE as well. With EDI-OCT, the choroid is thicker in eyes with CSC and there is expansion of the larger choroidal vessels (Imamura et al., 2009). The first instance of CSC has at least a 50% chance of spontaneously resolving, with minimal changes in vision as a consequence (Mohabati et al., 2020). With chronic or recurrent bouts of CSC, there can be increasing damage to the retina and RPE including atrophy of the retina and underlying RPE (Mohabati et al., 2018). CSC of any duration can cause decreased visual acuity, distortion, and color vision defects. Common sequelae of chronic CSC include atrophy of the outer retina and RPE and macular neovascularization. RPE atrophy is common in areas of long standing subretinal fluid. Capillary changes in the choriocapillaris may lead to decreased oxygen delivery. These changes may serve as risk factors for the development of macular neovascularization, either conventional neovascularization or polypoidal choroidal vasculopathy.

3.2.4.1. Risk factors associated with central serous chorioretinopathy. Over the course of more than 1 ½ centuries most of the theories of the pathogenesis of CSC have focused on two main underlying etiologies, the first is infection or the response to infection, and the second is the effects of stress and potential mediators of stress. In its first description, CSC was thought to be associated with syphilis, a common infection of the time (v. Graefe, 1866). Estimates of the prevalence of syphilis in pre-antibiotic 19th century London ranged from 9.3% to nearly 16% in males (Szreter, 2014). In the early 20th century Kitahara linked CSC to tuberculosis, which was a common infection in Japan at the time (Kitahara, 1936). More recently CSC has been linked to Helicobacter pylori infection, a common infection recognized in the modern era (Burucoa and Axon, 2017; Hunt et al., 2011).

In 2001, Giusti reported a patient with both H. pylori infection and CSC had resolution of the CSC upon treatment of the H. pylori (Giusti, 2001). Mauget-Faÿsse et al., (2002) raised the hypothesis of a focal ischaemia of the choriocapillaris due to the procoagulant effect of H. pylori by stimulation of mononuclear leukocytes (Mauget-Faÿsse et al., 2002). Some studies have suggested an ocular benefit from treating concurrent H. pylori infection (Dang et al., 2013; Zavoloka et al., 2016). Other studies found no improvement in the rate of the subretinal fluid or choroidal thickness (Atılgan et al., 2018; Horozoglu et al., 2018). These findings suggest H. pylori may have an association with CSC in some, but certainly not all, people with CSC. H. pylori is an extraordinarily common human infection and by chance alone would be expected in a large proportion of people with CSC even if there was no association between the two diseases.

The second broad theme of pathogenesis involves stress and associated factors as a risk for CSC. Horniker thought the disease to be caused by an angioneurosis causing angiospasm in the retina and exudation (Horniker, 1927), and used the name capillaro-spastic central retinitis. Gifford and Marquardt shared Horniker's view of a neurotic diathesis and coined the term central angiospastic retinopathy (Gifford and Marquardt, 1939). Harrington studied central angiospastic retinopathy in soldiers in World War II and concluded the disease was related to intense psychic trauma of war that caused sympathetic nervous system overactivity (Harrington, 1946). Bennett determined patients with central serous retinopathy had 'a tense obsessional "mental make-up", and a history of stress-producing life situations' (Bennett, 1955). Gelber and Schatz found an extraordinary 91% of patients with CSC had a preceding disturbing psychological event prior to the start of CSC (Gelber and Schatz, 1987). In a study of 57 patients with acute CSC as compared to age and sex matched controls, the most important psychological risk factor was perceived stress on the part of the patient (Sesar et al., 2020). CSC has been linked to Type A personality, depression, sleep abnormalities, and shift work (Bousquet et al., 2016; Ji et al., 2018; Yannuzzi, 1986).

The concept that there was sympathetic overactivity as a cause of CSC led to experiments, particularly in Japan, in which animals were given injections of adrenaline, cardazol (a stimulant that causes seizures), histamine, acetylcholine, or electric shocks to try to create a model of CSC (Ikeda et al., 1956). Some of these experimental treatments were thought to be non-specific stressors (Ikeda et al., 1956). Epinephrine had a theoretical advantage of being one of the hormones released during stress. Repeated adrenaline injections were physically stressful for the monkeys used in the experiment; in a study by Yoshioka and colleagues, half of the injected monkeys died (Yoshioka et al., 1982). De Venecia and coworkers clamped the renal artery in a monkey to induce hypertension (De Venecia et al., 1980). The monkey developed serous retinal detachments with multiple leaks during fluorescein angiography but later the eyes developed Elschnig spots consistent with the hypertension. Cheong et al. reported increase in choroidal thickness mainly attributable to choroidal vessel lumen based on OCT at 4 weeks and 8 weeks after administration of systemic adrenaline in monkeys. This was accompanied by leakage on ICGA (Cheong et al., 2021). Corresponding histology demonstrated dilated choroidal veins and choriocapillaris.

Theories related to infections and stress are not mutually exclusive. It is conceivable that infection can increase systemic or psychologic stress, or both. Conversely, stress causes changes in the hypothalamic–pituitary–adrenocortical axis and can lead to glucocorticoid receptor resistance (Cohen et al., 2012; Merkulov et al., 2017). The glucocorticoid receptor resistance renders subjects more susceptible to infection, and the amount of pro-inflammatory cytokines produced were greater in subjects with glucocorticoid receptor resistance (Cohen et al., 2012). Infection and stress can lead to altered hemorheological effects and alterations in signaling pathways in undoubtedly complex ways.

3.2.4.2. Dye-based angiography in central serous chorioretinopathy and revision of earlier theories. The source of the fluid in CSC has been controversial since its discovery. Earlier theories, such as by von Graefe, attributed the condition to an infection, in this case syphilis (v. Graefe, 1866). As mentioned in the previous section, theories of sympathetic overactivity and angiospasm later became more popular. The angiospasm was theorized to lead to secondary vascular leakage with accumulation of fluid (B.A. Klien, 1965).

A large change in the thinking about CSC came with a report of fluorescein angioscopy by Maumenee, which showed the leakage came from the level of the RPE, not the retinal vessels (Maumenee, 1965). Gass proposed in 1967 that CSC was secondary to choroidal vascular hyperpermeability (Gass, 1967) and changed the name to idiopathic central serous chorioretinopathy. Gass's contention of choroidal hyperpermeability was difficult to evaluate because of the lack of any method to image hyperpermeability. That opportunity occurred in 1986 when Hayashi and coworkers found that most eyes with CSC had ICG leakage from the choriocapillaris near the leak seen in fluorescein angiography (Hayashi et al., 1986). The authors proposed the leakage from the choriocapillaris was the result of RPE degeneration. Some of the eyes had a delayed filling, which the authors ascribed to a choroidal circulatory insufficiency. In 1993, Scheider and coauthors reported the fluorescein and ICG angiography findings of 19 patients with CSC (Scheider et al., 1993). In most of the patients, there was a delay in perfusion in the leaking area using ICG angiography. The authors stated the angiographic signs of choroidal vascular leakage stopped when the

disease became inactive. They proposed the leakage was the result of an infectious or vascular abnormality.

Later papers demonstrated that eyes with CSC had multifocal choroidal vascular hyperpermeability seen in the mid-phase of the ICG angiography sequence(Guyer et al., 1994; R. F. Spaide et al., 1996; R.F. Spaide et al., 1996). This finding was the unifying feature for many separate conditions ultimately shown to be variants of CSC. In addition, the ICG leakage was persistent following the resolution of clinically evident disease. The concept of identifiable regions of hyperpermeability was a driving force behind the development of photodynamic therapy (PDT) using verteporfin for the treatment of CSC (Lim et al., 2014a; Ober et al., 2005; Yannuzzi, Slakter, Gross, Spaide, Costa, Huang, Klancnik Jr., et al., 2003) as will be discussed in section 4.2.4.7.2. While hyperpermeability was an integral feature of the CSC variants, the etiology was unknown. In a publication in 1995, Prünte proposed there was delayed filling of choroidal vessels "followed by capillary and/or venous congestion" and leakage (Prünte, 1995). Prünte proposed that adjacent areas of ischaemia caused an inhomogeneous blood flow and congestion as a consequence. The venous congestion and increased pressure, associated with ischaemia, was proposed to result in excess leakage. Kishi and coworkers evaluated the correlation between the areas of filling delay in early-phase ICG angiography and the regions of dilated vortex veins in en face OCT imaging and found there was a significant co-localization (Kishi et al., 2018). They proposed that CSC may be a disease characterized by vortex vein congestion that developed in eyes with asymmetric vortex veins (Hiroe and Kishi, 2018; Kishi et al., 2018). Expansion of ideas concerning the pathogenesis of CSC will be presented in section 3.2.4.6.

3.2.4.3. Optical coherence tomography in central serous chorioretinopathy. The implication of choroidal vascular hyperpermeability was that excessive leakage of fluid from the choriocapillaris produced excessive hydrostatic pressure in the choroid. The early published reports of ICG angiography also showed that the choroidal vessels were enlarged. If the hydrostatic pressure is elevated and the choroidal vessels are enlarged, one would expect the choroid should be thickened. EDI-OCT confirmed that eyes with CSC had thickened choroids as well as an increase in the diameter of choroidal vessels, particularly of the larger veins in Haller's layer (Imamura et al., 2009). The choroid was seen to be abnormal not only in eyes with active CSC, but also in eyes with resolved CSC and even in fellow eyes in patients with unilateral CSC (Imamura et al., 2009). The ratio of the vessels' lumens (essentially only seen in the larger vessels) to the choroidal area was abnormal in eyes with CSC (Agrawal et al., 2016). In later phases of CSC, there appears to be a relative loss of Sattler's layer, while Haller's layer vessels remain distended.

3.2.4.4. Recent imaging findings in central serous chorioretinopathy. OCT also provided other clues concerning abnormalities in the choroid. Hiroe and Kishi proposed that there was an asymmetry of the choroidal venous drainage in eyes with CSC and that the choroidal veins were dilated (Hiroe and Kishi, 2018). Matsumoto and colleagues, looking at nearly identical en face OCT slab images, proposed that there were anastomoses between the inferotemporal and superotemporal vortex vein systems at the watershed zone in eyes with pachychoroid neovasculopathy (Matsumoto et al., 2019).

Later the anastomotic vessels between the inferotemporal and superotemporal vortex vein systems in pachychoroid neovasculopathy were observed in CSC and polypoidal choroidal vasculopathy (Matsumoto et al., 2020). An example of the slab OCT images of normal and intervortex venous anastomoses are shown in Fig. 6. Importantly, the authors evaluated only the posterior pole to the extent of the 12 × 12 mm image centered on the fovea would allow.

A study of wide-field ICG angiography of patients with CSC, peripapillary pachychoroid syndrome, and macular neovascularization including polypoidal choroidal vasculopathy associated with CSC found there were intervortex venous anastomoses in all patients (R.F. Spaide et al., 2020)(Fig. 7). The anastomoses in these ocular conditions occurred nearly uniformly among the superonasal, superotemporal, and inferotemporal vortex vein systems (Fig. 8). The inferonasal vortex vein was less often involved; it was seen to anastomose with the superonasal vortex vein but less often with the inferotemporal vortex vein. Findings in patients with peripapillary pachychoroid syndrome were different, as in this disease the intervortex venous anastomoses occurred among all of the vortex vein systems, but predominantly in the peripapillary region. In CSC, the anastomoses were primarily in the central macula. The neovascular cases showed the same patterns of anastomoses as those with CSC, which is not surprising given that the neovascular cases had pre-existing CSC. In some of the neovascular cases, anastomotic vessels were the predominant vessels seen in the macular choroid with no normal choroidal veins remaining in the macular region. The diameter of the anastomotic vessels could be as much as several hundred micrometers in diameter (R.F. Spaide et al., 2020).

Cheung and coauthors (Cheung CMG, Teo KYC, Spaide RF. Pulsatile filling of pachyvessels in watershed zones in pachychoroid disease. In press, Retina.) examined video frame rate ICG angiography, and also digital subtraction angiography (R.F. Spaide et al., 1998) of patients with CSC. They found there was a delay in filling of the choroidal veins, much like previous studies. However, they found the filling of the larger veins occurred in a pulsatile fashion over a widespread area of the macula, particularly in intervortex venous anastomoses. In several cases, there was an oscillatory flow during the cardiac cycle in which the direction of flow reversed. In a study of eyes with retinal vein occlusion, Paques and coworkers found there was pulsatile filling, with oscillatory periods, in retinal veins following retinal vein occlusion (Paques et al., 2005). The analogous finding in choroidal veins suggests a flow obstruction, but because these changes were found distributed in the macula, it did not appear that there was obstruction of a specific single vortex vein (Cheung et al.). Pulsatile filling of veins is seen in CCSF and vortex vein obstruction, as mentioned earlier.

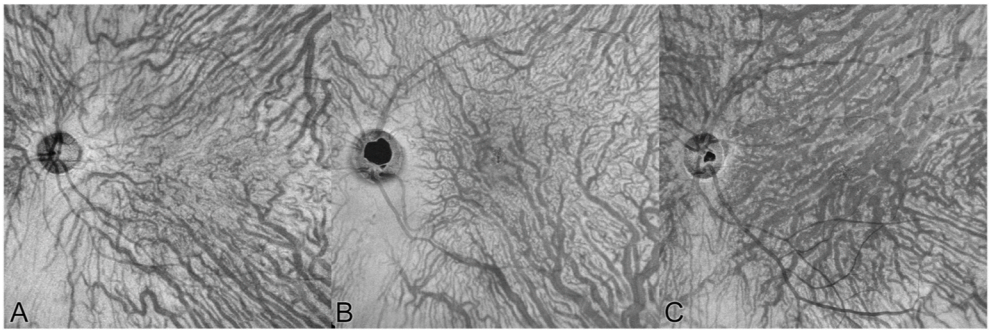

Fig. 6. En face OCT images (12 mm × 12 mm) in the deep layer of the choroid. Intervortex vein anastomosis is considered to be present if anastomotic vessels connected the superotemporal and inferotemporal vortex veins. The anastomotic vessels do not show narrowing toward the watershed zone. (A) Normal eyes usually show symmetrical superotemporal and inferotemporal vortex veins and a horizontal watershed zone. (B, C) CSC eyes usually show dilated vortex veins. The horizontal watershed zone has disappeared, showing instead collateral veins due to anastomoses between the superotemporal and inferotemporal vortex veins.

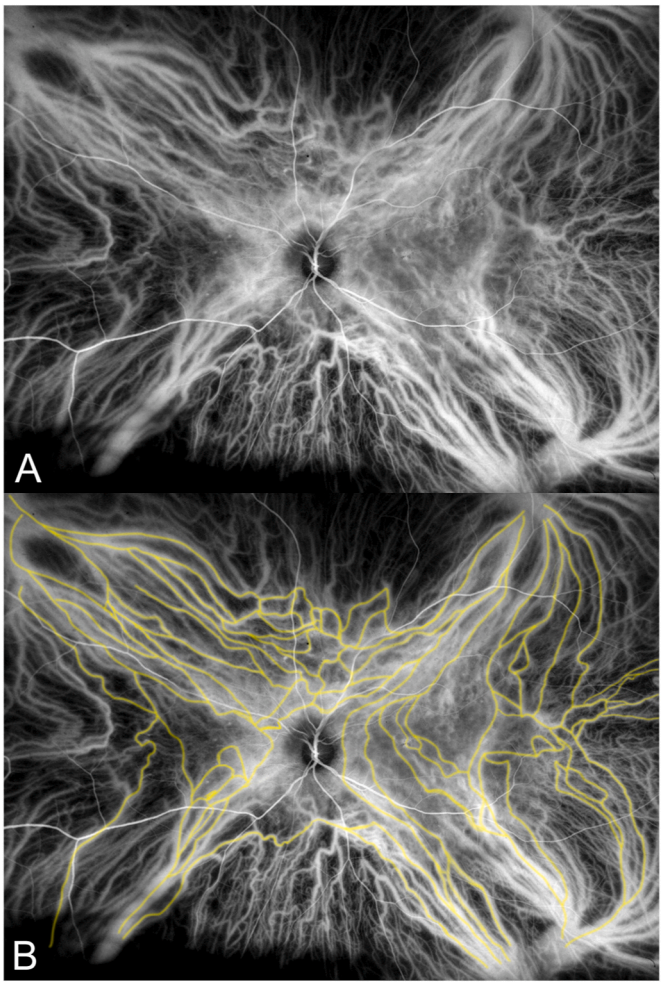

Fig. 7. A 49 year-old with central serous chorioretinopathy. A The patient has numerous intervortex venous anastomoses, some of which are highlighted in B) with yellow.

The leakage seen in ICG angiography occurred in regions at or near the anastomotic vessels (Fig. 9). Slow filling of some of the choroidal veins is seen over a wide area, including anterior to the equator (Fig. 10).

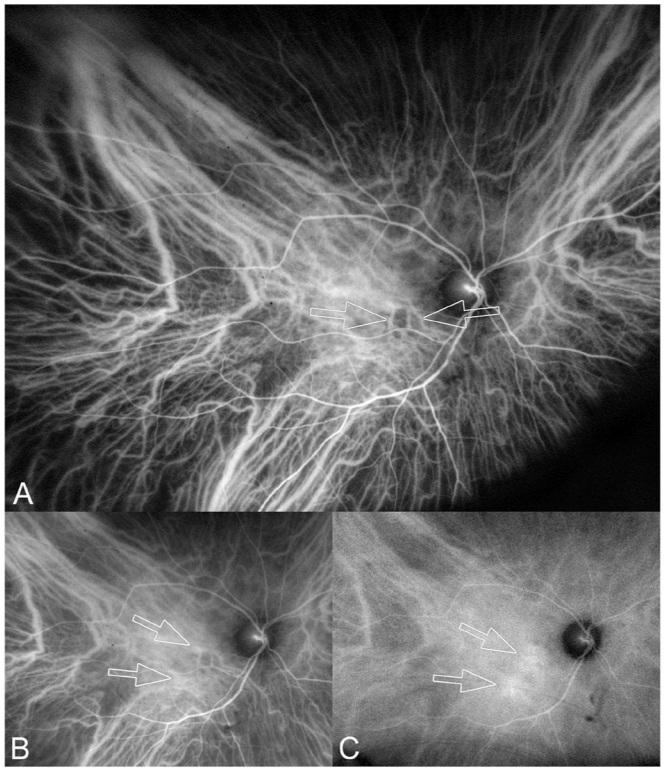

Fig. 9. Widefield ICG angiography of a patient with new onset central serous chorioretinopathy. Her brother and husband both died in the recent past and she developed a serous detachment of the macula a few months later. A. She had veins bridging across the macular region (open arrows). B. Increased fluorescence from leakage is seen 1 min 52 s after injection (open arrows) straddling the region of the intervortex venous anastomoses. C. By 4:36 after the injection the leakage in the choroid has expanded (open arrows).

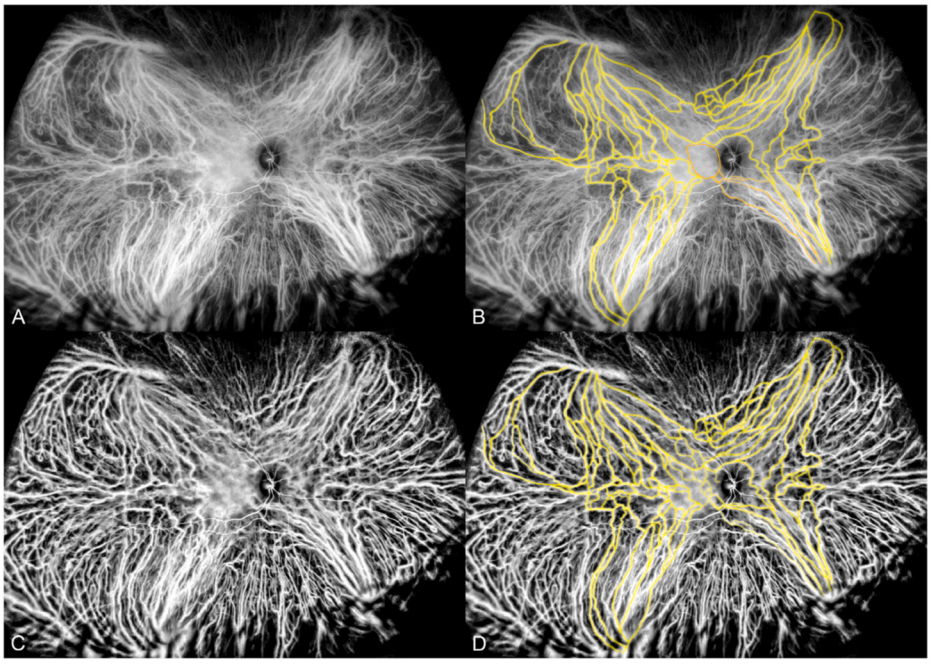

Fig. 8. Wide-field ICG angiogram of a 48 year-old with central serous chorioretinopathy. A. Image obtained 2:51 min after ICG injection. B. Some of the intervortex venous anastomoses are highlighted in yellow for easier recognition. There are a group of vessels, highlighted in orange, that lead to the inferior macular region and are no longer visible in the central macula because of early leakage (area surrounded by orange outline). C. Using wavelet contrast enhancement of he middle and low spatial frequency components, haze was removed from the image leaving clear delineation of the larger vessels. D. The central intervortex venous anastomoses are visible, as highlighted in yellow.

The areas of ICG hyperfluorescence are characteristically seen most easily from 10 to 20 min after injection. By this time, the liver has removed most of the dye from the blood stream, leaving any dye in the choroid to be visualized without vascular patterns. The actual dye leakage starts early. Fig. 11 shows two relatively early frames, one at 1:07 and the other at 3:24 after ICG injection. Subtraction of these two results in an image showing the difference, which is dominated by the dye that leaked during that interval. The late phase ICG at 20:05 after injection shows much broader, ill-defined areas of hyperfluorescence at the same locations as shown by the subtraction.

Using frame averaged OCT angiography, it is possible to image and also derive measurements of the capillaries of the choriocapillaris (Spaide and Ledesma-Gil, 2020). A study examined eyes with a history of CSC or peripapillary pachychoroid syndrome and compared them to normal controls. The disease entities "pachychoroid" or "pachychoroid spectrum" have numerous disparate definitions, many of which do not require a thick choroid despite the name (Spaide, 2020). To examine the characteristics of the choriocapillaris in eyes with a thick choroid, a third group, eyes having a choroidal thickness greater than the age-adjusted 95th percentile but no known ocular problems, were also examined (R.F. Spaide and Ledesma-Gil, 2020). Among the choriocapillaris parameters measured were mean capillary length, standard deviation of capillary length, capillary number, diameter, and fractal dimension. In all of the measured parameters the normal eyes and the age-adjusted 95th percentile plus thickness eyes showed no significant difference. On the other hand, in the CSC and peripapillary pachychoroid syndrome eyes the choriocapillaris showed reduced number of capillaries, which were longer, wider, and had a greater standard deviation than either the normal or the 95th percentile group. The fractal dimension was also lower (Spaide and Ledesma-Gil, 2020). These findings show that a thick choroid is not necessarily pathologic, and diseases such as CSC and peripapillary pachychoroid syndrome are associated with choriocapillaris abnormalities independent of choroidal thickness.

3.2.4.5. Relevant published pathology of central serous chorioretinopathy. There are several cases of serous macular detachment that ultimately went on to histopathologic examination. The histologic findings of two eyes were published by Klien in 1953 with what was thought to be central angiospastic retinopathy (B.A. Klien, 1953). An additional eye was later reported by Klien that had what was then called serous chorioretinopathy and included a re-evaluation of the previous two cases (Klien, 1961). These include a 50-year-old man who had a history of headaches and had blurring of his vision in the left eye for 4 or 5 weeks. The patient had a serous detachment of the macula and a flat slate-gray area descending inferiorly from the inferotemporal portion of the nerve and had a corresponding visual field defect. Because of the pigmentation, the patient was enucleated because of a suspicion of a malignant melanoma. The second case was a 45-year-old man who had presented with blurred vision in the right eye for 3 weeks. The patient also had a serous detachment but also a 1-disc diameter nevus in the same eye. The fluid did not resolve over an observation period of 4 weeks, and so the patient was enucleated for possible melanoma. The third patient was a 52-year-old man who had a 1-week history of blurred vision. The patient had a serous detachment and a 1.5-disc diameter slate gray discoloration, and since the fluid did not resolve over a 2-week observation period, his eye was enucleated for fear of melanoma. Importantly, no melanoma was found in any of the cases. After histopathological evaluation, these eyes were thought to have what is now called CSC, but evaluation of the published figures show the third case also had what appeared to be a fibrovascular lesion in the macula.

The first case had enormous dilation of the veins in the choroid, such that in one section (Fig. 12), the choroid was almost completely occupied by large veins. There were some lymphocytes and eosinophils in the choroid. The second case was thought to have marked dilation of the capillaries and veins in the choroid. There were some aggregates of leukocytes, particularly eosinophils in the choroid and more prominently involving the retrobulbar vessels. Although the histopathologic examination was not performed to modern standards, the findings suggest venous enlargement and remodeling, along with modest signs of inflammation.

3.2.4.6. Refinement of pathophysiologic theories of central serous chorioretinopathy

3.2.4.6.1. Influence of venous outflow. Many theories of CSC pathophysiology, at least from the time of ICG angiography, hinged on multifocal choroidal vascular hyperpermeability. This hyperpermeability was attributed to RPE degeneration, possible infection, vascular abnormalities, ischaemia from various causes including choriocapillaris compression, and congestion. With the more recent findings obtained by OCT, OCT angiography, and wide-field ICG, a refinement of past theories seems possible, especially with inclusion of pathophysiology involving venous drainage elsewhere in the body.

Findings common to reported ICG angiographic studies are venous dilation and a delay in vascular filling of the choroid. Intervortex venous anastomoses occurring in CSC, similar to those found in patients with CCSF and in eyes with mechanical occlusion of the vortex veins,

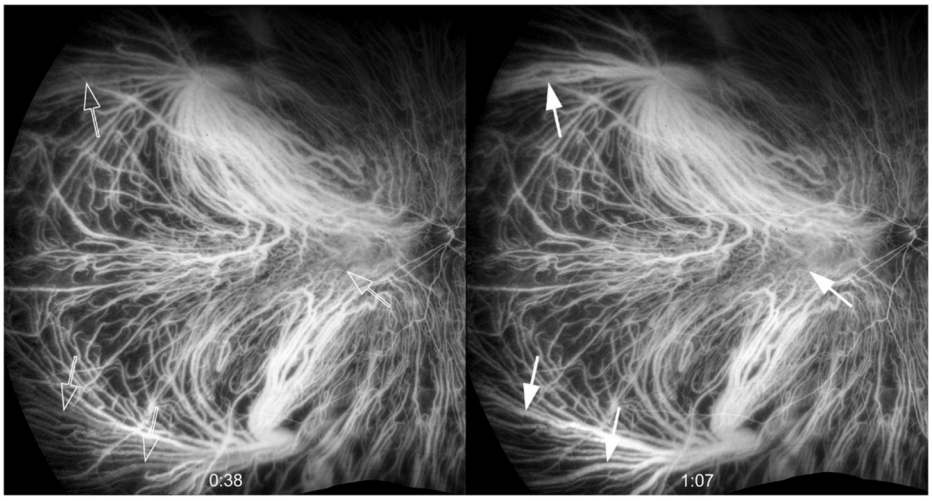

Fig. 10. The same patient as shown in Fig. 8. This figure illustrates there are veins in the choroid that fill slowly. In the left side, taken at 38 s after injection of ICG dye, shows veins that are relatively hypofluorescent as compared with their neighbors (open arrows). The picture on the right shows the same vessels (now highlighted with white arrows) are now as bright or brighter than their neighbors.

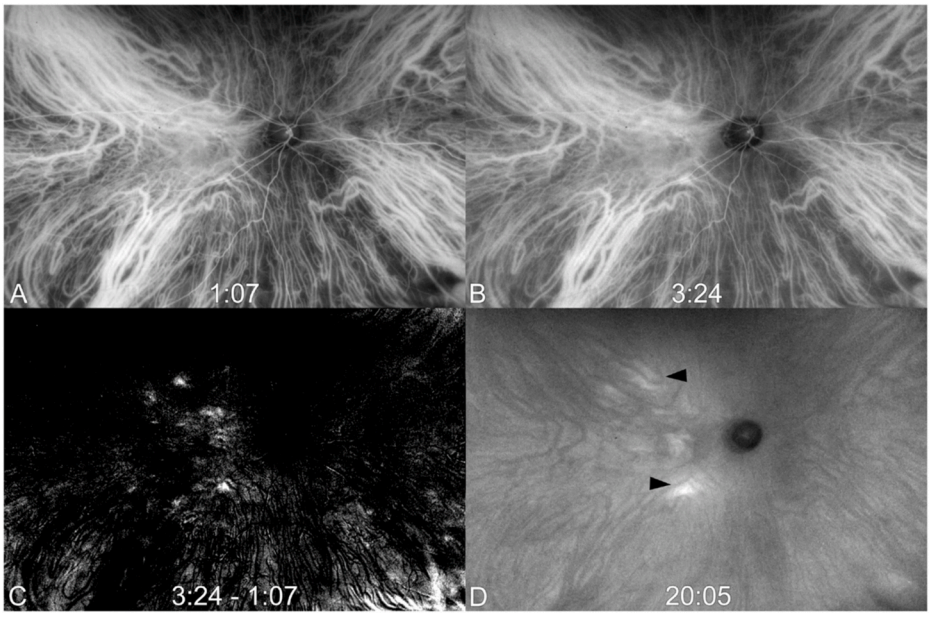

Fig. 11. Detection of dye leakage starting early in the ICG angiogram. A. This image, taken at 1:07 after ICG injection shows robust filling of the choroidal vasculature. B. This image was taken at 3:24 after injection and looks similar. C. Subtraction of the image in A) from that in B) shows small discrete bright areas. D. Later phase indocyanine green angiographic image shows ill-defined areas of hyperfluorescence in the choroid from the leakage. The larger choroidal vessels are dark, which implies the dye is between or behind the large vessels. The subtraction image highlights the areas in which the leakage was first visible.

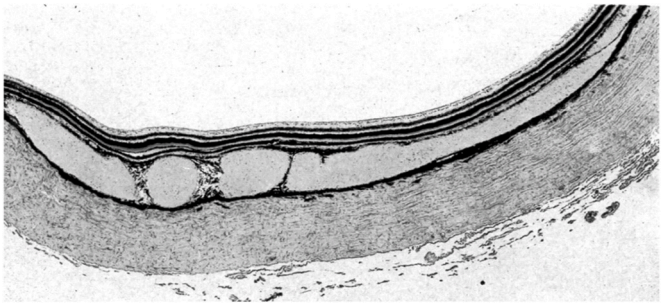

Fig. 12. This patient had a lobular slate grey discoloration extending inferior to the optic nerve and was enucleated with the diagnosis of malignant melanoma. No tumor was found. The patient was then thought to have 'serous chorioretinopathy'. There is enormous dilation and congestion of the choroidal veins. (From Klein BA Macular and extramacular serous chorioretinopathy. American Journal of Ophthalmology 1961, used with permission.)

reinforces the concept of problems with venous outflow in CSC. It is possible the flow abnormalities affect one (or more) of the vortex vein systems, leading to congestion and venous pressure increases. Anastomosis development to shunt flow into neighboring vortex vein systems could overload those as well. Whereas CCSF and vortex vein occlusion are caused by extraocular problems, CSC appears to have no associated extraocular abnormalities. This focusses attention to the local venous outflow from the eye. Although the veins draining the submacular choroid may lead to one vortex vein system preferentially (Fig. 13), for many eyes this is not true, and all eyes show multiple anastomotic venous connections that can be quite large. These findings suggest there is also a more generalized outflow problem of the entire outflow system, even if one or two vortex vein systems have a relative decreased outflow.

In venous systems throughout the body, increased venous pressure can lead to dilation and initiation of a cascade of events leading to venous remodeling. Abnormalities of venous outflow from the choroid may be expected to share pathophysiologic similarities with that seen in veins elsewhere in the body. It is possible that the anastomotic channels develop in part to divert blood flow from vortex vein systems that may have comparatively greater outflow abnormalities, and these same veins may dilate because of increased venous pressure using much the same pathophysiologic processes participating in CVI elsewhere in the body.

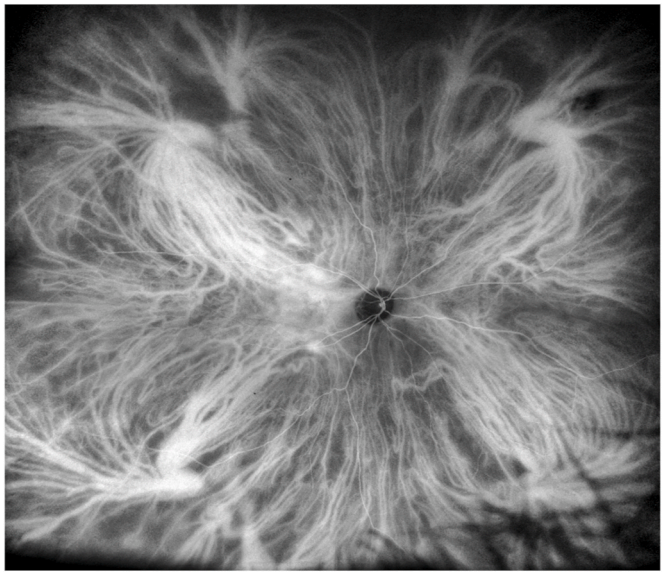

Fig. 13. There is a prominent enlargement of the superotemporal vortex vein system and anastomotic connections with a smaller inferotemporal vortex vein in this patient with CSC. In this eye a predominant amount of drainage of the macula region occurs via the superotemporal vortex vein system, but in other eyes there may be a more symmetrical drainage.

These processes would emulate those occurring in the formation of varicose veins, but to a lesser degree. These would include vascular remodeling and expansion with pooling of blood and increased venous backpressure that compounds the original venous outflow problems. While these changes are generic in their occurrence, they also may adversely affect the control of local venous pressure in the management of venous outflow. The dilated veins, augmented by the dilated anastomoses, could increase venous outflow pressure from the choriocapillaris leading to leakage from and damage to the choriocapillaris. Thus, the intrinsic abnormalities of outflow lead to a venous overload choroidopathy. In this scenario, the choriocapillaris problems are not directly related to venous compression of the choriocapillaris, a logical fallacy of *cum hoc ergo propter hoc* as the pressure in the choriocapillaris is higher than the choroidal veins. As will be discussed in the following

sections, there are many other inter-related factors to consider in the complete pathophysiologic picture of CSC.

3.2.4.6.2. Influence of the sclera. The findings in uveal effusion syndrome may help elucidate comparable findings in CSC. Increased choroidal vascular accumulation is visible during ICG angiography. Eyes with CSC are often hyperopic with a shorter axial length (Oh et al., 2014). While it is difficult to measure the posterior sclera thickness, Imanaga and coworkers reported the anterior scleral thickness was greater in eyes with CSC than in controls (Imanaga et al., 2021). The expectation was the posterior scleral thickness is proportional to the anterior scleral thickness. In CSC, as in any other choroidal vascular abnormality with increased fluid production in the choroid, there are no lymphatics to remove excess fluid. Instead, the excess fluid permeates through the sclera to leave the eye. The propensity for fluid to collect is dependent on leakage from vessels, potential absorbance by vessels and clearance through the sclera. Thickening of the sclera could have two effects. The first is that the permeability of a structure is a function of its thickness and the permeability per unit thickness. Increasing thickness would be expected to decrease the amount of fluid permeating the sclera. The second factor relates to the potential valve effect created by the course of vortex veins through the sclera. A thicker sclera would increase the length of vein compressed, potentially augmenting the Starling resistor effect (Fig. 4).

3.2.4.6.3. Balance of factors in fluid accumulation. The fluid exudation from the choroidal vessels appears to be greater in CSC, whereas the absorption is theoretically less, and the permeance of the sclera is decreased. Fluid has the potential to leak from the choriocapillaris as influenced by the permeability of the vessels, the feeding arterial pressure and the draining venous pressure. These factors may play a role in any potential fluid reabsorption by the choroidal vessels, as leakage occurs in discrete areas (Fig. 11). Fluid has the potential to leave by way of the sclera (Fig. 14). Modifying any of the triad of factors has the potential to change the propensity for fluid accumulation in the choroid. Increases in hydrostatic pressure in the choroid can lead to leaks at the level of the RPE into the subretinal space. In addition to contributing to sub-RPE or subretinal fluid in CSC, (or as subretinal or intraretinal fluid in peripapillary pachychoroid syndrome), the fluid may accumulate in pockets in the posterior choroid (R.F. Spaide and Ryan, 2015) or in intrachoroidal cavities (Sakurada et al., 2018).

3.2.4.7. Past treatments of central serous chorioretinopathy as refined by theories of pathogenesis. There have been a large number of treatments for CSC. Table 1 shows more than 65 different treatments that have appeared in the peer-reviewed literature. Each of these appear to have been guided by pathophysiologic theories of the time. Some may appear logical from a modern viewpoint. It is difficult to imagine what concepts of pathophysiology led to some of the treatments listed, such as injection of insulin-free pancreas extracts, ultraviolet light treatment of the sclera, or cocaine-adrenaline treatment of the nasal mucosa (see Table 2).

3.2.4.7.1. Laser photocoagulation and micropulse laser. The first treatment for CSC with consistent efficacy was laser photocoagulation starting in the 1960s (J.D.M. Gass, 1967; Peabody et al., 1968; Spalter, 1968). Ruby laser has a short burn duration, 200 μs (Peabody et al., 1968). This was supplanted by argon lasers in which the photocoagulation exposure could be controlled. Robertson and Ilstrup performed laser photocoagulation in eyes directly to the observed leak, indirectly in the eye away from the observed leak, or as a sham procedure (Robertson and Ilstrup, 1983). There was no difference in sham and indirect laser. The eyes treated with direct laser had the duration of their serous detachment reduced by approximately two months. The authors stated none of the laser treated eyes had a recurrence during an 18-month follow-up period (Robertson and Ilstrup, 1983). Some groups found reduced recurrences of subretinal fluid after laser photocoagulation (Burumcek et al., 1997; Yap and Robertson, 1996), while others did not (Brancato et al., 1987; Ficker et al., 1988; Gilbert et al., 1984). The aggregate of these studies seems to show decreased duration of subretinal fluid with no long-term improvement in acuity and no significant reduction in recurrences.

Micropulse laser has been used to treat CSC. Advantages of micropulse laser are its low cost and potential to be a non-damaging treatment. There are significant barriers to assessing the treatment as there is a huge variability in lasers and treatment strategies. This makes speaking of micropulse laser for CSC quite nebulous, since micropulse covers so many treatment possibilities (Altınel et al., 2021; Arsan et al., 2018; Büttner et al., 2021; Framme et al., 2015; Gawęcki et al., 2019; Işık et al., 2020; Özmert et al., 2016; Scholz et al., 2017; van Rijssen et al., 2019). In a generic sense, micropulse studies do seem to point toward anatomic and visual acuity improvement.

3.2.4.7.2. Photodynamic therapy. PDT with verteporfin was developed for ophthalmic use in treating macular neovascularization that could occur with age-related macular degeneration. The drug and laser dosing were first developed in animal models and then tested in humans to arrive at a recommended treatment (Husain et al., 1999). This treatment was seen to cause decreased fluorescence in the choroid, seemingly as a collateral damage (Schmidt-Erfurth et al., 2005, 2009). The modulation of choroidal ICG fluorescence raised the possibility of using PDT with verteporfin or ICG as the photosensitizing agent as a treatment for CSC, which was first done by several groups in different continents (Battaglia Parodi et al., 2003; Costa et al., 2002; Yannuzzi et al., 2003). In a comparative trial, laser photocoagulation and PDT were both found to cause a resolution of subretinal fluid in CSC eyes, with laser photocoagulation causing no change in choroidal thickness

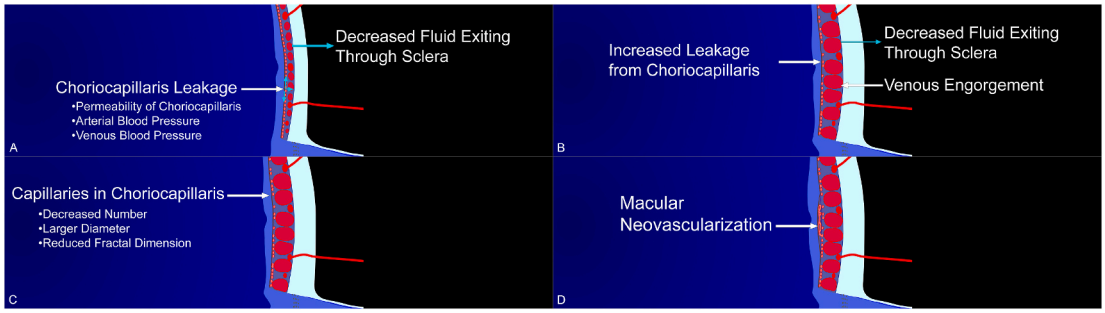

Fig. 14. Factors affecting fluid accumulation in central serous chorioretinopathy and allied disorders. A. In a normal eye, the amount of potential leakage from the choriocapillaris is affected by the arterial feeding pressure, draining venous pressure, and permeability of the choriocapillaris. Increasing any of those factors would increase the transudation. Similar factors apply to any vessels in the choroid. Excess fluid creased in the choroid has the potential of being removed by adjacent non-pathologic areas of perfusion or through fluid exiting the sclera. The amount of fluid capable of leaving the sclera is dependent on the thickness of the sclera, its permeability per unit thickness, and the pressure head driving the fluid flow. B. In CSC there is increased leakage from the choriocapillaris, dilation of the choroidal veins, and potentially decreased fluid leaving through the sclera. C. The capillaries in the choriocapillaris have a decreased number, larger diameter, greater diameter and a reduced fractal dimension as compared with normal eyes. D. In some patients, macular neovascularization develops.

Table 1
Treatments for central serous chorioretinopathy.

Acetazolamide	Micropulse laser (various forms)
Acetylcholine	Microwave therapy
Acupuncture	Mifepristone
Acycloguanosine	Multivitamins
Adrenocorticotropic hormone	Neostigmine
Aminophyllin	Nicotinic acid
Amyl nitrate	Nimodipine
Anisodine	Nylidrin hydrochloride
Antibiotics for H. pylori	Old tuberculin intracutaneously
AREDS formulation vitamins	Organic iodides
Aspirin	Papaverine
Benzyl imidazoline hydrochloride	Paveril phosphate
Beta-blockers	Phenobarbital sodium
Betamethasone	Photodynamic therapy with indocyanine green
Bevacizumab	Photodynamic therapy with verteporfin
Calcium lactate	Pyridyl carbinol
Centella asiatica	Rifampin
Cocaine-adrenaline treatment of the mucosa of the nose	Rutin
Cortisone	Sodium nitrate
Drug electrophoresis	Sodium tetrathionate
Dicoumarin	Spironolactone
Epleronone	Streptopenicillin injections
Estrogen	Sun gazing
Ethylmorphine	Theobromide
Finasteride	Thyroid hormone
Grid laser photocoagulation	Tissue extract
Hydrochlorthiazide	Triamcinolone
Ibuprofen	Typhoid vaccine
Insulin-free pancreas extract injections	Ultraviolet light baths
Interferon alpha 2a	Ultraviolet light to the sclera
Ketaconazole	Vitamin B complex
Laser photocoagulation to leak	Vitamin C
Melatonin	Xenon arc photocoagulation
Methotrexate	

There have been many treatments for CSC, each presumably based on a concept of disease pathophysiology.
(Araki et al., 2019; Bandello et al., 1998; Beck et al., 2003; Bennett, 1955; Bhatti et al., 1986; Caccavale et al., 2009; Chung et al., 2013; Dang et al., 2013; Edwards and Priestley, 1964; Forooghian et al., 2011; Fusi-Rubiano et al., 2020; Gärtner, 1987; Gifford, 1944; Gifford and Marquardt, 1939; Gonzalez, 1992; Gordon et al., 1951; Govetto et al., 2019; Gramajo et al., 2015; Hobbs, 1953; Huang et al., 2019; Ichihasi, 1961; Jonas and Kamppeter, 2005; Lewczuk et al., 2019; Li P., 1985; X. Q. Li et al., 2015; Loewenstein, 1941; Lotery et al., 2020; MacLean and Brambel, 1947; Nehemy et al., 2010; Nicolò et al., 2020; Nielsen and Jampol, 2011; Ober et al., 2005; Paul and Leopold, 1956; Pecora, 1978; Ratanasukon et al., 2012; Rathschuler et al., 1990; Roseman and Olk, 1988; Scheider et al., 1991; Tatham and Macfarlane, 2006; R. Venkatesh et al., 2018; Yannuzzi, Slakter, Gross, Spaide, Costa, Huang, Klancnik Jr. et al., 2003; Zavoloka et al., 2016).

while PDT decreased the choroidal thickness by approximately 15% (Maruko et al., 2010). Later study showed the choroidal stroma decreases in thickness and as do the Haller layer vessels following PDT (Sonoda et al., 2016).

The macular neovascularization dose for PDT worked, but randomized trial suggested using half of the laser light dose may offer improved risk versus benefit outcomes (Bae et al., 2014; Semeraro et al., 2012; Zhao et al., 2015). A large number of case series studying the use of PDT in the treatment of CSC were published as has been previously reviewed (Lim et al., 2014b; van Rijssen et al., 2019). Randomized controlled studies of varying sizes found patients receiving PDT did better than those getting a placebo (Chan et al., 2008; Wu et al., 2011). The trials comparing PDT to anti-vascular endothelial growth factors were underpowered and no conclusions could be made about relative efficacy (Bae et al., 2014; Semeraro et al., 2012). PDT was compared to micro-pulse laser in two trials, both showing improved efficacy with PDT (Kretz et al., 2015; van Dijk et al., 2018). In a study of the long-term follow-up of patients receiving PDT or micropulse laser for CSC, there were fewer recurrences in the eyes treated with PDT, but no statistical difference in ETDRS letters gained, retinal sensitivity, or NEI-VFQ25 quality of life scores (van Rijssen et al., 2021).

Table 2
Previously described features, novel data, and new interpretations in central serous chorioretinopathy.

Previously Described Features	Novel Imaging Data	Novel interpretation
Enlarged choroidal veins	Widefield ICGA demonstrated intervortex anastomosis. Dynamic ICGA demonstrated pulsatile filling within anastomotic segments	1. Increase venous pressure leads to venous remodeling 2. Anastomoses create blood filled reservoirs that do not adequately drain, and contribute to choriocapillaris loading caused by regional venous dilation
Choroidal filling delay (ICGA)	OCTA showed reduced number of capillaries with lower fractal dimension within Choriocapillaris	3. Vascular expansion, pooling and increased venous backpressure
Uveal effusion eyes tend to have thick choroid and short axial length	Increased anterior scleral thickness in eyes with CSC	4. Decreased fluid permeating the sclera 5. Increased resistance of outflow in vein exiting the eye (Starling's resistor)
Choroidal hyperpermeability (ICGA)	In regions of the posterior pole near intervortex venous anastomoses	6. Generalized venous outflow problem
Increased choroidal thickness	OCTA showed choriocapillaris features comparable to normal eyes in eyes with thick choroid but no pathology. Eyes with CSC or peripapillary pachychoroid syndrome have choriocapillary changes	Thick choroid *per se* is likely an epiphenomenon and not primary disease cause. Thick choroid may be seen with no pathology, or in other diseases, such as CSC and peripapillary pachychoroid syndrome. Thick choroid may be seen in inflammatory diseases, e.g. Vogt-Koyanagi-Harada disease, but the natural history of such conditions is entirely different from venous outflow choroidopathy.

In monkeys treated with PDT, marked reduction of choroidal thickness was observed, with more predominant reduction in the choroidal stroma than vascular lumen. Choriocapillaris damage was noted from hypofluorescence within the treatment spot on ICGA and loss of fenestration in corresponding histological specimens (Cheong et al., 2021). Current treatment of CSC with PDT using verteporfin demonstrably changes the choroidal leakage as imaged by ICG angiography, but not the underlying outflow obstruction and vascular remodeling. Recurrence of neurosensory detachment may occur, particularly if the underlying venous outflow problem remains un-addressed. Conceivably the other factors contributing to disease manifestations discussed above are modifiable as well.

3.2.4.7.3. Modifying scleral outflow. Scleral windows have been used to treat CSC (Machida et al., 1997; Maggio et al., 2020; P. Venkatesh et al., 2016). Machida and coworkers examined repeat ICG angiograms in 4 eyes that were treated by scleral windows and found no change in vascular characteristics even though the subretinal fluid resolved. Thus, the outflow was improved without apparent changes in the vascular parameters (Machida et al., 1997). A broader overview of modifiable factors will be presented in Section 5.

3.2.5. Peripapillary pachychoroid syndrome

Phasukkijwatana and colleagues described peripapillary pachychoroid syndrome, which they defined as: 1) intraretinal and/or subretinal fluid in the nasal macular region extending from the temporal margin of the optic disc as noted with OCT and 2) a thicker choroid than would be expected for age potentially associated with Haller vessel dilation and overlying inner choroidal thinning (Phasukkijwatana et al., 2018). Although there are many conditions that could fulfil that definition, the cases shown appear to have had B-scan OCT findings of the choroid that place this condition in the CSC family. It is not apparent why peripapillary pachychoroid is a syndrome, while CSC is not. In a study evaluating wide-field ICG angiography, patients with peripapillary pachychoroid syndrome had numerous, prominent intervortex venous anastomoses in the peripapillary region. These patients may also have PEDs. It is likely this condition is a variant of CSC, sharing the underpinnings of dilated choroidal veins, intervortex venous anastomoses, choroidal vascular hyperpermeability, and fluid exudation (R.F. Spaide et al., 2020). The salient difference is that the vascular problem occurs near the optic nerve in peripapillary pachychoroid syndrome, and there is expansion of the choroid and also of the juxtapapillary retina. At the termination of the retina near the optic nerve is a layer of glial cells known as the intermediary tissue of Kuhnt and this continues as a separation between the choroid and nerve as the layer of Jacoby (Hogan et al., 1971). These layers serve to insulate the nerve, choroid, and retina from one another. The expansion of the juxtapapillary retina and choroid likely alters this barrier function, allowing fluid ingress into the retina, as is seen in this disorder. Otherwise, the same underlying venous drainage abnormalities as is found in CSC appear to be operative in this condition.

3.2.6. Spaceflight associated neuro-ocular syndrome

After long space flights, most astronauts experience one or more changes in the eye and brain including optic disc oedema, choroidal thickening and folding, hyperopic refractive shifts, a peculiar type of globe flattening, enlargement of the optic nerve sheaths, optic nerve swelling, and ventricular enlargement in the brain (Lee et al., 2020a; Nelson et al., 2014; L. F. Zhang and Hargens, 2018). This disorder is known as spaceflight associated neuro-ocular syndrome or SANS. In post-flight questionnaires, reported degradation in near vision occurred in 29% of astronauts for short duration shuttle and 60% for long duration International Space Station missions (Mader et al., 2011). The IOP increases by 5–7 mm Hg on entry to space (Nelson et al., 2014; Wostyn et al., 2019). The CSF expands the arachnoid space in the optic nerve sheaths, creating a pear-shape enlargement abutting the globe. The flattening of the posterior portion of the globe may persist even years after return to earth. The choroidal thickening may become less pronounced on return to earth, but the choroidal thickness does not necessarily return to normal (Lee et al., 2020b; Mader et al., 2011).

The microgravity environment in the orbiting craft has a lack of forces to move venous blood to flow down from the head or the CSF down to the spinal canal. Instead, there is a shift of blood and CSF toward the head, as compared with terrestrial physiology (Dreha-Kulaczewski et al., 2017). Within minutes to hours of being in space, facial tissues swell, there is nasal congestion, and astronauts may experience mild headaches. With the cephalic shift in fluid, the intracranial pressure spikes are thought to cause temporary headaches. Returning astronauts have increased ventricular volume in the brain, and these changes partially reverse on earth (Roberts and Petersen, 2019a). The alteration in the ventricles has been compared to hydrocephalus. This change may be the result of a microgravity analogue of hydrocephalus (Roberts & Petersen, 2019a, 2019b). Features in common with terrestrial idiopathic intracranial hypertension include papilloedema, perioptic nerve sheath distention, buckling of the optic nerve, globe flattening, pituitary concavity, and empty sella (Hingwala et al., 2013). Arguments have been made against hydrocephalus, in part on the basis that hydrocephalus is associated with prolonged, severe headaches, pulse synchronous tinnitus, double vision, photopsia, and ophthalmic imaging findings (Williams and Malm, 2019; Wostyn and de Deyn, 2018).

In parabolic flight studies in which simulated microgravity occurs, the choroidal blood volume doubles within seconds (Nelson et al., 2014). In space, the choroid thickens, there is a hyperopic shift and development of chorioretinal folds occurs. In spaceflight, thickening of the retinal nerve fiber layer also occurs and uncommonly, cotton wool spots form. The increased intracranial and IOP in conjunction with the cephalad displacement of blood would be expected to alter both the venous outflow from the brain and eye. The altered blood and fluid distribution would make pressure buffering from venous outflow less effective. Loading of the subarachnoid space around the optic nerve may alter local physiology. These considerations may help explain the congested appearance of the optic nerve in SANS.

Terrestrial investigations to help gain insight into SANS have been done using head down tilting tables to emulate the cephalad displacement of blood (Kergoat and Lovasik, 2005; Laurie et al., 2017; Marshall-Goebel et al., 2017; Rim et al., 2015; Shinojima et al., 2012). This subject is also of interest because of positioning during surgical procedures (Grant et al., 2010). The choroid becomes thicker within minutes and becomes increasingly thick over time. The intraocular pressure also increases, likely related, in part, to increased choroidal volume and increased pressure in the venous veins. The translaminar pressure decreases(Laurie et al., 2017) and the ocular pulse pressure also decreases (Kergoat and Lovasik, 2005).

4. Venous overload choroidopathy as a disease

Alterations in the venous drainage of the eye have potential to affect the retina and choroid. Because of readily visible changes, the changes associated with abnormalities of venous drainage affecting the retina have been evaluated over many years and are not the focus of this manuscript. The choroid can suffer consequences of abnormalities in venous drainage and there is much less foundational knowledge. Advances in imaging has allowed greater depth and areas of the choroid to be evaluated and has helped increase our knowledge of the involved pathophysiology. Venous outflow abnormalities caused by CCSF or vortex vein occlusions produce a set of findings including venous dilation, choroidal hyperpermeability, and intervortex venous anastomoses. These eyes had extraocular reasons for the venous outflow abnormalities. SANS also has extraocular reasons for outflow abnormalities but are related to alterations in microgravity and other factors related to spaceflight such as hypercapnia and elevated CSF. CSC and peripapillary pachychoroid syndrome show similar venous findings as CCSF or vortex vein occlusions, but have no extraocular factors affecting venous drainage. Analysis of the vascular physiology of the choroid suggested that there could be abnormalities in local control of venous outflow. All of these disorders have the possibility of inducing the observed venous changes such as dilation, abnormal amounts of remodeling, and anastomosis formation on the basis of pathophysiologic venous changes seen elsewhere in the body (Fig. 15). These changes may remain subclinical if short-lived or mild. However, with increasing severity, duration, or both, these choroidal changes may cause manifest secondary problems, such as atrophy of the retina or RPE related to fluid accumulation, macular neovascularization, and so forth.

By putting these factors together, it is possible to find an organising linkage for the disease pathophysiology of venous overload choroidopathy (Fig. 16). This organizational structure also helps in classifying disease. The concept of pachychoroid has been used to organise some choroidal disease entities in the past. There are several problems with the logic behind the terms pachychoroid and pachychoroid spectrum (Spaide, 2020). There are numerous definitions for pachychoroid and all elements in the pachychoroid spectrum, many of which would classify normal eyes as being pathologic. The origin of the term pachychoroid was rooted in the choroid being thick, but the concept was later changed to include eyes in which the choroid was not thick. Many entities that

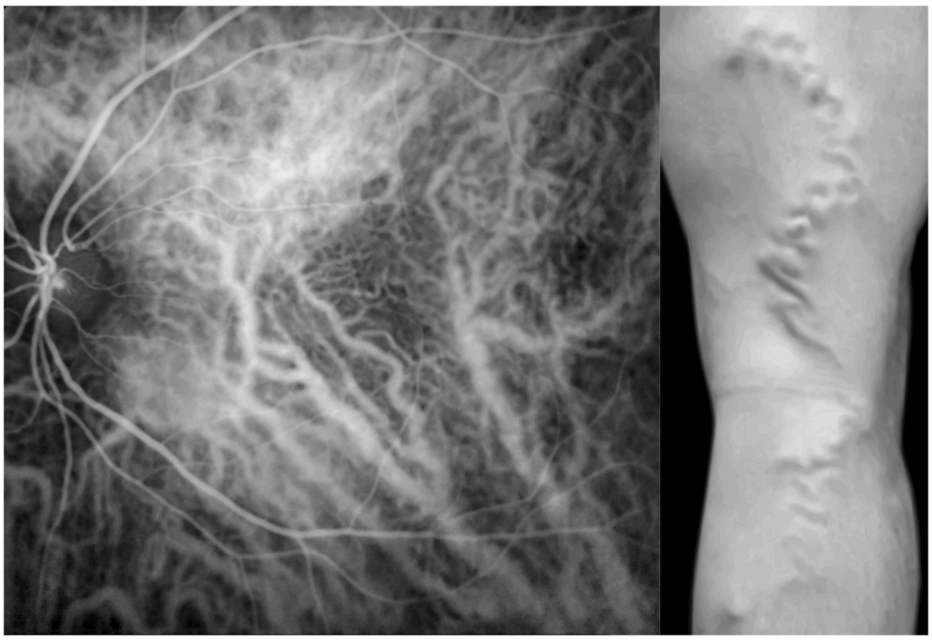

Fig. 15. Chronic central serous chorioretinopathy versus varicose veins. On the left is a 60 year-old patient with chronic central serous chorioretinopathy. The normal pattern of larger choroidal veins is not present. There is an interlocking network of a few dilated tortuous veins linking vortex systems. While these are not the same size as the vessels in the vortex veins in the leg (right) some of the same pathophysiologic processes may be shared in the venous remodeling of both organ systems.

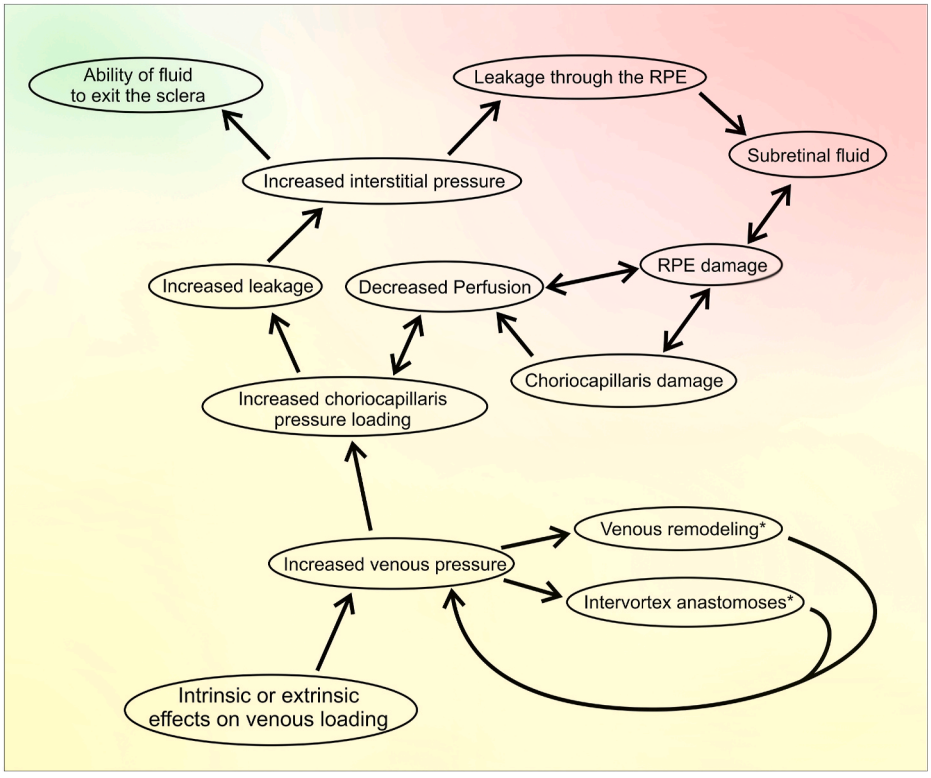

Fig. 16. Pathways to subretinal fluid leakage related to venous overload choroidopathy. Intrinsic or extrinsic effects on venous loading cause increased venous pressure and increased loading of the choroidal vessels. Although the focus of this diagram is the effects on the choriocapillaris, leakage could potentially come from other vessels as well. Venous remodeling and intervortex venous anastomoses may develop initially through compensatory mechanisms but are potentially detrimental to larger purposes in the choroid. At some phases of the systolic/diastolic pressure cycle these changes may serve to increase venous back-loading in the choroid. The steps that may occur without clinically observable manifestations are shown with a yellow background and those with clinically evident pathological manifestations are shown with a red background. The ability for fluid to leave through the sclera can potentially decompress the choroid and is shown with a green background.

cause choroidal thickness were not included (R.F. Spaide, 2020). Choroidal vascular hyperpermeability was suggested to be an important feature, but there is a large number of entities that cause choroidal vascular hyperpermeability that are not included in the pachychoroid spectrum (R.F. Spaide, 2020). Finally dilated choroidal veins were considered to be an important feature, but there are many causes of dilated choroidal veins that are not incorporated in the pachychoroid spectrum set of conditions.

The World Health Organization published a best practices guideline for naming medical diseases (Fukuda et al., 2015). Among the many recommendations were that the name should include generic descriptive terms, be specific, short, and include the pathologic cause.

Pachychoroid, although short, is not specific and is not a cause of problems, rather it is an epiphenomenon. Venous overload chorioretinopathy is a descriptive, specific name that identifies the underlying pathology that leads to a shared set of ocular abnormalities. The linking features in these diseases are not just a clinical finding that may be present, but a unifying pathophysiology. Although the mechanisms causing venous overloading vary, the defined pathophysiology allows for the proposal of methods for their repair.

5. Future directions for research and possible new treatments

The diseases covered share compelling similarities in pathophysiology and uniting these commonalities into a broader theory of pathogenesis. A theory has the potential to explain or inform, but logical extension of a theory leads to predictions. Mechanistic theories also bring gaps of knowledge into critical focus. By accurately defining some of the pathogenic process, the areas where more work is needed are obvious. No prior theory could adequately explain why males are more commonly afflicted with CSC. The present proposal notes the venous outflow from the choroid may be modulated according to the passage of the vortex veins through the sclera to form a Starling resistor. The effect would seem to be dependent on scleral thickness. Men have a greater scleral thickness than women (Buckhurst et al., 2015; Read et al., 2016; Schlatter et al., 2015). On the other hand, eyes with CSC have a thicker scleral thickness than normal and, in these eyes, there are no sex differences. This suggests scleral thickening is a risk factor for CSC and males, by virtue of having thicker sclera, may have a higher risk. In those with CSC the sclera is thick no matter what the sex is. This is an interesting avenue for future research. Systemic corticosteroids and Cushing disease are associated with CSC (Araki et al., 2019; Carvalho-Recchia et al., 2002; Tittl et al., 1999; van Dijk et al., 2016). Curiously, there is no sex predilection in corticosteroid related CSC (Araki et al., 2019). Of the thousands of doses of intravitreal corticosteroids given, CSC is a distinctly uncommon side-effect (Noh et al., 2019).

The proposed theory centers on venous overload and physiologic consequences induced in the choroid (Fig. 16). While treatment of carotid cavernous sinus fistulas and AVMs is directed against the offending source, a similar focus is lacking for CSC. The most successful treatment so far is PDT, which has the potential to damage, perhaps in mostly a good way, the choriocapillaris. However, PDT does not specifically address the source of venous obstruction. Longer term, atrophy is an important consequence of this treatment (Lim et al., 2014b). A rarely performed procedure for CSC is the creation of scleral windows, which attempts to address the outflow through the sclera in focal locations. With interest in the venous drainage from the choroid as a mechanism of disease, surgical procedures involving the vortex vein may be a potential treatment modality. Any surgical approach has to consider the possibility of inadvertent injury to a vortex vein. Vortex vein decompression in the method of Brockhurst is another possibility (Bouzas et al., 1993; Brockhurst, 1980). It may be possible to do relaxing incisions or perform small wedge resections of the sclera near the vortex vein to decrease any compressive force on the vortex vein. For most patients, the relative safety of PDT using verteporfin is an overwhelming attribute, but PDT is not successful in everyone. Another possibility is to perform laser panretinal photocoagulation of the retina peripheral to the temporal equator. This would decrease the visual field, but to the far nasal area, occupied by the bridge of the nose. It is possible this would decrease blood loading from the anterior choroid into the temporal vortex vein systems, thereby reducing choroidal congestion in the macula. This latter method is destructive and less desirable. While these procedures all have limitations, the new understanding of the disease mechanism outlined in this review should lead to design and evaluation of novel therapies that specifically address the venous obstructive aspect of this group of conditions.

The treatment for peripapillary pachychoroid syndrome has not been established. A fortuitous aspect of peripapillary pachychoroid syndrome is that many patients do not have subfoveal fluid, and the visual acuity in untreated patients can be relatively good. A retrospective review of 43 eyes treated with seven different therapies (anti-vascular endothelial growth factor injections, PDT, focal macular laser, oral or topical carbonic anhydrate inhibitors, or topical or intravitreal corticosteroids) unsurprisingly showed no significant improvement in visual acuity (Xu et al., 2020). Given the pathophysiology proposed in the present paper, PDT would be a prime choice to evaluate in a treatment study.

Additional research needs to be performed to understand the frequency and nature of intervortex venous anastomoses in health and disease. While it is common to detect anastomoses in eyes with CSC, their origins are not well understood. In some patients, anastomoses are likely to be expansions of pre-existing channels and not the growth of new vessels. In other eyes, there appear to be so many anastomoses that it seems possible they were already present as dilated channels and a watershed zone never existed in the first place. Fig. 17 shows an interesting patient who developed CSC at an early age. The wide-field ICG shows a myriad of intervortex venous anastomoses. It is possible this patient had many of these anastomoses present as a developmental abnormality that later led to CSC.

The most efficient mechanism to evaluate anastomoses at present is with wide-field ICG angiography in which the fundus up to the vortex vein ampullas can be captured in a single image. ICG angiography is an invasive procedure with risks that are low, but not zero. With the speed in developments of OCT technology, evaluation of larger regions of the choroid will become increasingly efficient. Currently evaluation of the possibilities of anastomoses is done by piecing mental images of slab images together. Automation of this analysis may allow for automatic evaluation of patients for the tendency to progress to these diseases. This may also be interesting to implement this in the International Space Station, which has an OCT device.

In SANS, the extra loading of blood into the venous pressure in the eye may cause some of the same choroidal vascular changes as have been noted in patients with CCSF or CSC, namely the development of intervortex venous anastomoses. Some of these changes, particularly the venous dilation and anastomoses, may not reverse on return to earth. This produces a testable hypothesis that could be evaluated by wide-field ICG angiography of astronauts pre- and post-space flight for intervortex anastomoses, choroidal vascular hyperpermeability, and choroidal filling delays. Establishment of dilated choroidal veins with potential of intervortex venous anastomoses may establish a pathologic state in the choroid that may make some aspects irreversible.

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Declaration of competing interest

Richard F. Spaide - Topcon Medical Systems, Regeneron, Roche,

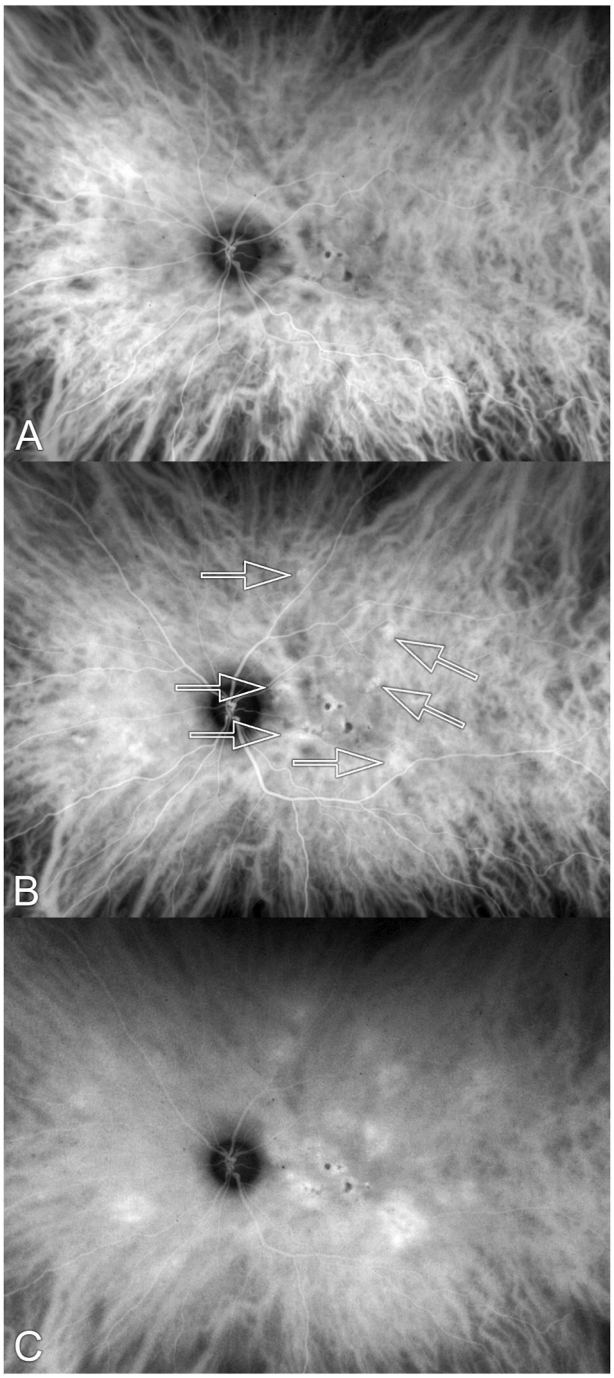

Fig. 17. Widespread intervortex venous anastomoses in a 31-year-old. A. At 32 s after indocyanine green injections an enormous number of intervortex venous anastomoses were imaged. B. By 1:31 min after injection areas of leakage are already visible (open arrows). C. The leakage is more evident at 5:50 min after injection.

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